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Some Properties of the *N*-Cinnamylephedrines, and the Analysis of Aspirin, Caffeine and Cinnamylephedrine in Admixture*

By Llewellyn H. Welsh and George L. Keenan†

The isomers of 1-phenyl-2-methylcinnamylaminopropanol-1, $C_6H_5CHOHCH(CH_3)N(CH_3)CH_2CH = CHC_6H_5$, are included in a group of substances described as "alkamines" or "phenylalkylolamines" which are the subjects of United States (1) and British (2) patents. These patents attribute anesthetizing and spasmolytic properties to the molecule of the above structure, and it has been indicated elsewhere in the literature (3) that 1-phenyl-2-methylcinnamylaminopropanol-1 (cinnamylephedrine) has a vasodilatory action. Aside from the references cited, no further information concerning the *N*-cinnamylephedrines has been encountered in the literature. Since at least one cinnamylephedrine isomer has been used in pharmaceuticals, it seemed desirable to supplement the meager information available in order to make possible the satisfactory identification of these substances.

The *N*-cinnamylephedrines may exist in two enantiomorphic forms corresponding to *d*- and *l*-ephedrine, and also in a racemic modification.[1] The three forms were prepared in good yields by the action of cinnamyl chloride on the corresponding ephedrines. As recorded in the patent literature, the precipitation of unsubstituted ephedrine as the hydrohalide accompanied the substitution of the cinnamyl radical. This was obviously due to the combination of excess ephedrine with the hydrogen chloride liberated during the replacement of amino hydrogen by the cinnamyl radical. It seems probable that the deposition of ephedrine salts reported as occurring in solutions of the base in chloroform (4) and other reactive organic halides (5) was the result of a similar reaction, the nature of the radical substituted for the amino hydrogen being dependent upon the particular halide involved.

* The portion of this paper concerning the analysis of the drug mixture was presented at the Pre-convention Meeting of the U. S. Pharmacopœial Convention, Washington, D. C., 1940.

† Food and Drug Administration, Federal Security Agency, Washington, D. C.

[1] The patents referred to cover substances having a certain chemical structure and, therefore, include not only compounds having an ephedrine-like configuration, but also those corresponding to the pseudoephedrines. This paper is concerned only with compounds spatially related to the ephedrines.

It does not appear likely that the deposition of ephedrine salts in the cases cited was due to the ability of the base to abstract hydrogen halide from the halide solvent (5).

Replacement of the amino hydrogen atom of ephedrine by a cinnamyl radical produced a product which rotated the plane of polarized light in a direction opposite to that characteristic of the ephedrine employed. Thus, the product from *d*-ephedrine was lævorotatory, and that from *l*-ephedrine was dextrorotatory in alcohol or benzene solutions. Such an effect has been observed in the synthesis of other *N*-substituted ephedrines, *e. g.*, benzylephedrine (6), a vinylog of cinnamylephedrine.

The optically active and inactive free bases were obtained easily in beautifully crystalline condition. The inactive hydrochloride was sufficiently well crystallized to permit the estimation of optical crystallographic properties, but the corresponding active salts were obtainable only in a microcrystalline condition. The crystallographic data which were determined are enumerated later.

As evidenced by the action of several typical alkaloidal precipitants on solutions of the racemic hydrochloride (Table I), the cinnamylephedrines respond to such reagents at considerably lower concentrations than do the ephedrines. Under the conditions of these tests, no crystalline products were formed. The precipitates were of an oily, resinous or amorphous nature.

One characteristic of the hydrochlorides of the *N*-cinnamylephedrines and, apparently, of the sulfates of these bases, is their solubility in chloroform. This solubility is relatively high, particularly in the case of the optically active hydrochlorides, when compared with the ability of most alkaloidal salts to dissolve in this solvent. The distribution of the cinnamylephedrines between diluted mineral acids (hydrochloric, sulfuric) and chloroform is of such a nature as to render impracticable their quantitative retention in the aqueous phase during extraction with chloroform. This is due to solubility of the salts in chloroform rather than to their hydrolysis. For this reason, the usual procedure for the quantitative separation of caffeine from other alkaloids and organic bases is not applicable to mixtures of caffeine and a cinnamylephedrine.

A procedure has been developed for the assay of a preparation containing aspirin, caffeine and cinnamylephedrine which permits the use of a single weighed portion of the mixture for the estimation of these three ingredients. Briefly, the method is to hold back the aspirin with cold, dilute bicarbonate, extract the caffeine and cinnamylephedrine base with chloroform and determine gravimetrically the combined weights of these two substances. The titer of the mixed residue gives directly the amount of cinnamylephedrine present, since caffeine has no titratable basicity under the conditions of assay. Aspirin is determined gravimetrically after extraction from the acidified bicarbonate layer. The gravimetric determination of aspirin, as such, in pharmaceutical preparations was originally described by Hitchins (7), and has subsequently been applied by Berman (8) and Grove (9). The assay is open to the objection that the value obtained for caffeine is subject to any errors arising from the titration procedure.

EXPERIMENTAL

Synthesis of Cinnamylephedrines.—These compounds were prepared by a method essentially that described in the patent literature, except that cinnamyl chloride was used instead of the bromide. Under these conditions, it was necessary to reflux the reaction mixture for six hours in order to obtain a maximum yield. Six Gm. (0.0363 mole) of the anhydrous ephedrine and 2.92 Gm. (0.0191 mole) of cinnamyl chloride in 23 cc. dry benzene were refluxed on the steam bath. After about five minutes the ephedrine hydrochloride began to precipitate. After six hours of refluxing, the ephedrine salt was filtered off, washed several times with a total of 75 cc. of benzene, and dried. The recovered salt amounted to 0.017–0.018 mole; melting point 216–217° (uncorr.) for the active hydrochlorides and 188–189° (uncorr.) for the racemic substance. The combined washings and filtrate from the precipitate where shaken with an excess of dilute sulfuric acid. A heavy, oily, orange-yellow layer (probably the sparingly soluble sulfate of cinnamylephedrine) separated and was drained off along with the aqueous phase into a separatory funnel. The benzene solution was shaken with three additional 100 cc. portions of dilute acid which were combined with the first extract. Sufficient water was added to dissolve

the oily layer (the volume at this point was about 600 cc.), and the acid solution was washed with benzene, made ammoniacal and extracted with chloroform. After evaporation of the chloroform, the residue was dissolved in 160 cc. hot alcohol-water mixture (53% by volume of ethyl alcohol) and cooled slowly, with shaking and seeding, to 5° C. The white needles were filtered off and dried in vacuum over sulfuric acid. Yields of 70–75% (based on the halide) were obtained. The melting point of the crystals was not appreciably changed by subsequent recrystallizations from alcohol-water or 30–60° petroleum ether. In reactions involving larger quantities of reactants, it was found more convenient, instead of using the extraction with acid, to concentrate the filtrate and washings from the precipitated ephedrine hydrochloride, and precipitate the cinnamylephedrine by gradual addition of 30–60° petroleum ether. This treatment removed most of the unreacted cinnamyl chloride and ephedrine base, and the crude product thus obtained was recrystallized from a suitable quantity of alcohol-water mixture.

The cinnamylephedrines were easily soluble in benzene, acetone, ether, chloroform and ethyl acetate; less soluble in alcohol and carbon tetrachloride; slightly soluble in petroleum ether and very slightly soluble in water. They were recrystallized twice more from alcohol-water to obtain pure samples for analysis, and the thrice recrystallized substances used in determining properties and constants.

N-Cinnamyl-l-ephedrine.—A sample of the substance gave a neutralization equivalent of 281 (calculated 281.4 for $C_{19}H_{23}NO$), and had the following properties: melting point[2] 85.6–85.7° (softened at 85.4°); $[\alpha]_D^{20}$ +24.6° (in benzene, $c = 10$, $l = 2$; preliminary work on 2% alcoholic solutions gave values of +10–11°). In ordinary light, under the microscope, the substance consisted of needles and rods (Fig. 1). Refractive indices were determined by the immersion method in potassium-mercuric iodide solutions: $n_\alpha = 1.582$ (shown lengthwise on rods and needles); n_β = indeterminate; $n_\gamma = 1.733$ (shown crosswise on rods and needles; methylene iodide could be used for this determination); both values ±0.002. Immersion media consisting of suitable mixtures of potassium-mercuric iodide, glycerol and water were found most satisfactory for the optical study of this substance, it being somewhat soluble in organic mixtures consisting of monochlornaphthalene and methylene iodide, although for rapid determinations the latter series was suitable. Most of the needles and rods yielded n_α lengthwise and n_γ crosswise. The birefringence was very strong. In parallel polarized light (crossed nicols) the extinction was parallel and the sign of elongation was negative. The rods and needles invariably extinguished sharply with crossed nicols. No interference figures were observed in convergent polarized light (crossed nicols).

Fig. 1.—*N*-Cinnamyl-*l*-Ephedrine (×150).

N-Cinnamyl-dl-ephedrine.—This substance was of the same crystal habit as the active isomers (Fig. 1). A sample yielded a neutralization equivalent of 282 and melted at 66.7–67.7° (softened at 66.5°). Mixed melting-point determinations on mixtures of the racemic and active bases in several different proportions gave initial melting at temperatures within the melting range observed for the racemic base. This might indicate the inactive base to be a pseudoracemic mixed crystal or of eutectic composition rather than a true compound. In ordinary light, under the microscope, this substance consisted of small needles and rods. In determining refractive indices, the same immersion media used in the study of the *l*-ephedrine derivative were found suitable: $n_\alpha = 1.570$ (invariably shown lengthwise; potassium-mercuric iodide-glycerol medium); n_β = indeterminate; $n_\gamma = 1.733$ (methylene iodide), shown crosswise on rods and needles; both values ±0.002. In parallel polarized light (crossed nicols), the extinction was parallel and the sign of elongation negative. The birefringence was quite strong. No interference figures were observed in convergent polarized light (crossed nicols).

N-Cinnamyl-d-ephedrine.—A sample gave a neutral equivalent of 282 and had the following constants: melting point 85.6–85.7° (softened 85.5°); $[\alpha]_D^{20}$ −24.7° (in benzene, $c = 10$, $l = 2$).

Cinnamylephedrine Hydrochlorides.—These compounds were prepared by the dropwise addition of ethereal hydrogen chloride to a solution of 2.00 Gm. of the purified base in 20 cc. benzene until a slight excess of acid was present. During addition of the

[2] Unless described as uncorrected, all melting points were taken using Anschutz-type thermometers previously tested by the National Bureau of Standards, and are corrected for stem exposure. They were observed while heating slowly (one-half degree or less per minute) from a temperature about 10 degrees below the point of fusion.

ether solution, the mixture was stirred and seeded to prevent deposition of the salt as a glassy film. After standing fifteen minutes, the white powdery hydrochloride was filtered off and washed with benzene. Yields were practically quantitative.

The optically active hydrochlorides were recrystallized by dissolving in 80 cc. boiling U. S. P. ethyl acetate and cooling slowly. Attempts to prepare these substances in a crystalline condition suitable for optical examination were not successful. Among methods tried were cooling of hot, saturated solutions in alcohol, water and chloroform, and precipitation from chloroform solutions by addition of ether or benzene. The racemic hydrochloride was recrystallized by dissolving in a boiling mixture of 150 cc. ethyl acetate and 45 cc. chloroform, and slowly cooling the solution.

These compounds were not appreciably soluble at room temperature in benzene, ether, acetone, carbon tetrachloride or ethyl acetate, but were somewhat soluble in alcohol, chloroform and water. The optically active salts were more easily soluble in chloroform, water and hot ethyl acetate than was the racemic salt. All tended to form supersaturated solutions from which they were slowly deposited, and rapid removal of solvent frequently left the hydrochloride behind as a resinous film which slowly assumed the state of a white solid. The substances had a bitter taste and exerted a strong anesthetic action on the tongue.

Fig. 2.—Racemic Cinnamylephedrine Hydrochloride (×150).

The racemic hydrochloride melted at 180.5–182°, with preliminary browning and shrinkage at 178°, and on analysis gave a value of 11.04% chlorine (calculated 11.16 for $C_{11}H_{24}ClNO$). In ordinary light, under the microscope, it consisted of irregular plates which broke up into angular fragments (Fig. 2). Its tendency was to occur in overlapping aggregates of plates. For determination of refractive indices, immersion media consisting of a series of mixtures of monochloronaphthalene and methylene iodide were most suitable; n_α = 1.550; n_β = indeterminate (probably shown on plates tipped on edge); n_γ = 1.733; both ±0.002. In parallel polarized light (crossed nicols), most of the fragments extinguished sharply, and the birefringence was very strong. In convergent polarized (crossed nicols), partial biaxial interference figures were occasionally shown.

The optically active salts consisted of microcrystals which tended to aggregate into small, irregular lumps. A sample of the *l*-ephedrine derivative gave an analysis of 11.03% chlorine and melted at 164–168°; its enantiomorph gave a value of 11.09% chlorine and melted at 163.5–168.5°. Before melting, both began to brown and shrink at 158–159°. Although the melting ranges were somewhat wider than that of the racemic salt, the active salts were, apparently, of the same degree of purity as that substance, since the residue from a chloroform solution of equal weights of the enantiomorphs melted at 180.5–182°, the temperature range recorded for the racemic salt.

Precipitation and Color Tests.—The following table lists results obtained in tests using several typical alkaloidal precipitants and a 1% solution of *dl*-cinnamylephedrine hydrochloride.

Table I.—Results of Precipitation and Color Tests

Reagent	Result	Approximate Minimum Concentration Responding to Reagent[a]
Saturated mercuric chloride	White ppt. consisting of oily droplets	1:350
Platinic chloride T.S.	Amorphous, yellowish ppt.; coagulates on shaking	1:2000
Gold chloride T. S.	Yellow ppt. consisting of oily or resinous material	1:10,000
Phosphotungstic acid, 1%	Heavy, flocculent light gray ppt.; coagulates slowly	1:10,000
Silicotungstic acid, 1%	Resembles phosphotungstic acid ppt.	1:10,000
Saturated alcoholic picric acid	Canary-yellow ppt.; deposits opaque resin on shaking	1:15,000
Mercuric potassium iodide T.S.	Resembles mercuric chloride ppt.	1:50,000
Iodine and potassium iodide T.S.	Red-brown ppt.; deposits dark brown droplets on standing	1:100,000

[a] The figures in this column represent the concentration in a solution of alkaloidal salt which yielded an easily visible turbidity or opalescence within a few second when ten drops of this solution were tested by adding from a fraction of a drop up to ten drops of the reagent. In some cases (*e. g.*, picric acid, platinic chloride, mercuric potassium iodide and iodine-potassium iodide), excess reagent seemed to destroy the turbidity, while in others (*e. g.*, gold chloride) the turbidity or opalescence was formed only at higher concentrations of the reagent.

When 0.01 Gm. of the cinnamylephedrine was dissolved in 1 cc. of concentrated sulfuric acid, there resulted red solutions having a faint orange tint. Addition of one crop concentrated nitric acid

to such solutions changed this color to amber, whereas addition of one drop of formaldehyde T.S. very greatly intensified the red color. One cc. of nitrosylsulfuric acid (prepared by dissolving 1.17 Gm. sodium nitrite in 15 cc. ice-cold concentrated sulfuric acid) when added to 0.01 Gm. of these compounds gave an intense brown color which was completely destroyed, with the attendant evolution of oxides of nitrogen, by addition of two volumes of water. With this reagent, ephedrine gave a light to medium brown color. Solutions of the hydrochlorides of the cinnamylephedrines (1%) gave the following reactions:

1. Addition of 10% potassium ferricyanide solution yielded a yellow precipitate (probably the ferricyanide of the base) which coagulated on shaking. The precipitate was dissolved on shaking with chloroform, and evaporation of the chloroform layer yielded a yellow, resinous film having a faint odor of benzaldehyde.

2. Dropwise addition of bromine water gave yellow precipitates which coagulated into small, orange resinous masses on shaking. Continued addition of reagent yielded additional precipitate which was increasingly difficult to coagulate.

3. Addition of 5% mercuric acetate drop by drop gave a white precipitate which dissolved in excess reagent. On boiling the resultant solutions, an odor resembling that of cinnamic aldehyde was observed.[3]

4. With cold potassium permanganate or boiling, alkaline potassium ferricyanide reagents, an odor of benzaldehyde was emitted. The odor was apparent even when 1 cc. of 1:20,000 solutions of the salts were used with an equal volume of reagent.

5. In the biuret test, modified according to Feng, the cinnamylephedrines gave results comparable with those recorded by that author for several other *N*-substituted ephedrines (6). To a mixture of 1 cc. of a 1% solution of the hydrochloride and an equal volume of 1% copper sulfate, 1 cc. of 20% sodium hydroxide was added. There resulted a violet color and voluminous precipitate. After shaking with ether, there separated a colorless ether layer and a clear aqueous layer having a faint bluish tint.

Analysis of Aspirin, Caffeine and Cinnamylephedrine in Admixture.—Racemic cinnamylephedrine base was found to undergo neither a detectable loss of weight or titer on drying one-half hour at 80°, although the substance melts somewhat below this temperature. Unlike ephedrine, a secondary amine, it does not react with chloroform under ordinary conditions. A solution of the base in chloroform, after one month of standing, suffered no loss of alkalinity such as would result from formation of the hydrochloride. Chloroform solutions of ephedrine deposit crystals of the hydrochloride on standing even for short periods of time.

The aspirin and caffeine used in the assay were of U. S. P. quality, the latter having been dried to constant weight, and the cinnamylephedrine hydrochloride employed was the optically inactive substance previously described. The powdered sample (consisting of 1.500 Gm. aspirin, 0.100 Gm. caffeine and 0.0500 Gm. cinnamylephedrine hydrochloride) was placed in a separatory funnel, 15 cc. cold water added and the mixture agitated until the powder was well wetted. Fifteen cc. of cold bicarbonate solution (prepared by dissolving 3 Gm. sodium bicarbonate in 45 cc. water at 15° or below and adding two or three drops dilute hydrochloric acid) were added, the separator swirled until the aspirin had completely reacted and the caffeine and cinnamylephedrine extracted with five 30 cc. portions of chloroform. Each extract was washed in a second separator containing 4.5 cc. water and 0.5 cc. strong ammonia water before filtering through cotton previously moistened with chloroform into a suitable vessel. The combined extracts were reserved for future use.

The determination of aspirin was carried out as soon as possible (to prevent undue hydrolysis) by the following procedure. The ammoniacal wash water was made acid with hydrochloric acid (1 + 1), added to the bicarbonate solution of aspirin, and the whole rendered acidic by adding more acid (approximately 10 cc. of 1 + 1 hydrochloric acid). The aspirin was completely extracted with chloroform, the extracts filtered through cotton into a tared container and evaporated on the steam bath in a current of air to a volume of 10 cc. The evaporation was continued to dryness in the air current, but without heat, and the residue allowed to stand in a desiccator for several hours or over night before being weighed. The residues could be checked by titration or bromination if desired. The aspirin residues obtained by this method were not distinguishable in melting point from U. S. P. aspirin, although tests for free salicylic acid were positive. Assuming 100% recovery of aspirin and the salicylic acid formed by hydrolysis, the difference between the weight of the residue weighed as aspirin and the amount of aspirin originally present indicated the hydrolysis of the ester to be less than 4% after remaining in the alkaline solution approximately one hour.

The chloroform containing the caffeine and cinnamylephedrine base was evaporated to a small volume on the steam bath, transferred quantitatively to a tared 50-cc. beaker and evaporated to dryness. After drying the residue one-half hour at 80°, it was weighed as cinnamylephedrine base plus anhydrous caffeine. An excess of 0.02*N* sulfuric acid was added and the residue dissolved by the aid of warming. The judicious use of a small amount of chloroform greatly facilitated solution, but it was entirely expelled by warming before titrating the excess acid with 0.02*N* sodium hydroxide in the presence of one drop methyl red T.S. Each cc. of 0.02*N* acid is equivalent to 0.006357 Gm. cinnamylephedrine hydrochloride or 0.005628 Gm. of the free base. From the titration figure, the amount of free base weighed with the caffeine was calculated and the

[3] Private communication from M. W. Tapley, Sterling Products Company, New York, N. Y.

weight of caffeine computed by difference. Results obtained by the method are listed in Table II.

Table II.—Results of Analysis of Aspirin, Caffein and Cinnamylephedrine in Admixture

Aspirin		Caffeine		Cinnamylephedrine HCl	
Recovery, Gm.	Recovery, %	Recovery, Gm.	Recovery, %	Recovery, Gm.	Recovery, %
1.494	99.6	0.100	100	0.0498	99.6
1.491	99.4	0.101	101	0.0497	99.4
1.493	99.5	0.101	101	0.0488	97.6
1.492	99.4	0.101	101	0.0486	97.2
1.490	99.3	0.100	100	0.0493	98.6
1.487	99.1	0.100	100	0.0495	99.0
1.487	99.1	0.100	100	0.0496	99.2
1.487	99.1	0.100	100	0.0495	99.0
Av.	99.3		100		98.7

The direct titration of the cinnamylephedrine-caffeine residues may be carried out in 50% alcohol, but the indicator is so affected by the medium that results are reliable only when one is thoroughly familiar with the end-point under such conditions.

When applied to tablets containing lubricants, the method must be modified to obtain correct recoveries of caffeine. The residue of caffeine, cinnamylephedrine and lubricant may be taken up with acid, the grease or wax removed by shaking with petroleum ether or a little benzene, and the cinnamylephedrine and caffeine recovered by extraction from the aqueous layer after rendering it ammoniacal.

For qualitative purposes, cinnamylephedrine base may be separated from caffeine by leaching the mixture with carbon tetrachloride or ether, in which caffeine is but slightly soluble, filtering, evaporating the solvent and recrystallizing the residue from alcohol-water mixture.

SUMMARY

(1) The preparation of the *N*-cinnamylephedrines by the action of cinnamyl chloride on the corresponding ephedrines has been described, and some properties of the bases and their hydrochlorides have been observed and recorded.

(2) A method for the separation and estimation of aspirin, caffeine and cinnamylephedrine in admixture has been described.

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Toxicity of Red Squill Powder and Extract for Chickens, Rabbits and Guinea Pigs*

By J. A. Lubitz and C. R. Fellers

INTRODUCTION

It is believed that red squill powder is non-toxic to some animals (hogs, dogs, cats, chickens) due to an emetic principle present in the red squill powder. This principle causes emesis when red squill is taken in toxic quantities, thereby preventing poisoning. The belief behind the specific raticide action of red squill is that rats have no vomiting mechanism and so cannot rid their systems of squill. Therefore, they become poisoned when squill is ingested in considerable quantity. It is interesting to note that according to Dukes (1) the act of vomiting is not common to all species of animals. Rodents, ruminants and solipeds seldom or never vomit, whereas carnivores and omnivores (except such as are rodents) vomit readily.

This work was conducted to determine the effect of a red squill extract on guinea pigs, rabbits and chickens, for there was doubt expressed as to the supposed harmless character of red squill extract baits to animals other than rats.

REVIEW OF LITERATURE

References in the literature (2, 3, 4) indicate that red squill is not readily taken by animals other than rats, and if consumed the emetic principle in the

* Contribution No. 389, Massachusetts Agricultural Experiment Station, Amherst.

squill causes vomiting, which usually saves the animal.

Munch, Silver and Horn (2) report the following: "Squill powders were mixed with whole-milk powder, and various proportions were added to 100 Gm. of lean, hashed meat, which was then fed to cats. In food containing 10 to 25 parts of squill powder per million the unusual flavor was detected, and the food was eaten slowly but completely.

"Dogs refused ground meat containing 1000, 2500 and 5000 parts of squill powder per million of meat. When squill powder suspended in water was injected into the stomach by stomach tube, emesis and diarrhea followed in several instances after doses of 100 mg. per Kg. of body weight. As dogs refused food containing a small concentration of squill powder, such as 1000 parts per million, it does not seem that they would be hurt by squill. Two separate instances have been noted where dogs gulped down squill rat baits containing 10 per cent of squill mixed with sausage. Emesis was the only effect noted.

"No effect was observed following the injection into chickens' crops of quantities less than 2000 mg. of squill powder per Kg. of body weight. Diarrhea followed the injection of 2000 and 3000 mg. per Kg. Squill powder was mixed with cracked corn and with laying mash in 10 per cent concentrations. Chickens refused to eat such food. Two chickens were placed on a diet containing 10 per cent of squill powder in growing mash. After refusing to eat for several days, they consumed the mash without much hesitation. This food was continued for two weeks, during which time the chickens apparently grew as well as controls fed on untreated mash.

"Pigeons refused to eat mash containing 10 per cent of squill powder. Injection of 2000 mg. of squill powder per Kg. of body weight into the crop failed to produce any noticeable effect. The injection of 3000 and 4000 mg. per Kg. resulted in emesis, but no other untoward effect could be noted.

"'A dose of 250 mg. of squill powder per Kg. was given in a gelatin capsule to a 4-month-old pig weighing about 16 Kg. The pig became ill but recovered in about two days after the feeding.

"Injected in aqueous suspension into the stomach of woodchucks, the minimum lethal dose of a sample of squill was found to be 500 mg./Kg. (the same as for rats). Vomiting, however, frequently followed even smaller doses. Baits containing squill were refused.

"Prairie dogs and pocket gophers refused to eat freshly exposed squill baits."

Koller (5) in his book reports that the toxic doses of a fresh squill sample given by Hubner are as follows: cats 200 mg./Kg., dogs 1500 mg./Kg., rabbits 3500 mg./Kg., guinea pigs 6000 mg./Kg., and hens 35,000 mg./Kg.

Ward, Barber, Garlough and Munch (4) report that red squill powder and red squill extract are toxic to hogs when given by stomach. They also state that most hogs will not eat enough red squill rat poison voluntarily to cause death, and that red squill powder causes emesis in hogs which tends to protect the animals when baits are consumed normally.

According to Mills (6) (unpublished data in his files) Read's laboratory in London ran a series of tests with squill powder having a lethal dose of 800 mg./Kg. on rats, and gives the following as toxic doses: cattle 300 to 500, pig below 300, fowl about 1000, rabbit above 1000 and guinea pig between 400 and 500 mg./Kg.

Silver and Munch (7) report that a human subject swallowed 15 gr. of a toxic red squill powder with no apparent harm, and later took 40 gr., which caused nausea and vomiting within 15 minutes, but no other effect.

EXPERIMENTAL

SQUILL SAMPLES

The red squill extract used in this work had a toxicity of 900 mg./Kg. when fed to male albino rats. The red squill powder used had a toxicity of 800 mg./Kg. when fed in the same way. For this work the red squill samples were diluted with water so that they could be conveniently pipetted. The diluted samples were fed orally by pipette to guinea pigs, rabbits and chickens at various dosage levels.

Toxicity to Guinea Pigs.—Guinea pigs were fed at 6300 mg./Kg., 1800, 900, 450 and 200 mg./Kg. levels with the diluted red squill extract. This red squill extract was fatally toxic to guinea pigs on all of the feeding levels.

The guinea pigs underwent the same type of rolling convulsion as do rats suffering from red squill poisoning. No vomiting was observed. The results of this feeding test indicate that guinea pigs are much more susceptible to poisoning by red squill extracts than are rats.

In like manner, guinea pigs were fed red squill powder on 100 mg./Kg., 200 and 300 mg./Kg. levels. Diarrhea was observed in most of the guinea pigs after the squill feeding. At the 100 mg./Kg. level 2/4 guinea pigs died, at the 200 mg./Kg. 0/2 died and at the 300 mg./Kg. level 3/3 died. We can conclude that guinea pigs are more susceptible to red squill powder than are rats.

Toxicity to Rabbits.—Rabbits were fed the red squill extract using the same technique as with guinea pigs. Three feeding levels were used: 450 mg./Kg., 900 mg./Kg. and 1800 mg./Kg. The rabbits evinced no untoward effects from the squill extract feeding. No vomiting was observed. We may, therefore, conclude that levels of red squill extract which are definitely toxic to rats seem to have no harmful effects on rabbits.

Red squill powder was fed to rabbits at levels of 1600 mg./Kg., 2400 mg./Kg. and 3200 mg./Kg. The rabbit on the 2400 mg./Kg. level succumbed and the rabbits on the other two levels were affected but survived. The indication is that rabbits are

very resistant to squill poisoning but very high feeding levels may be toxic. These rabbits underwent the same type of rolling convulsion as do rats preliminary to recovery or death from red squill poisoning. No vomiting was observed.

Toxicity to Chickens.—Chickens were also fed red squill extract in like manner. The feeding levels used ranged from 450 mg./Kg. to 4500 mg./Kg.

This experiment indicates that red squill extracts are non-toxic when fed to chickens, even in very large amounts.

Red squill powder was fed to chickens on the following levels: 2400 mg./Kg., 3200 mg./Kg., 4000 mg./Kg. and 4800 mg./Kg. No discomfort was observed following the squill powder feeding. This corroborates the findings of other investigators relative to the innocuous character of red squill powder when fed to chickens.

DISCUSSION

Rats, guinea pigs, rabbits and chickens are unable to vomit. However, rats and guinea pigs are susceptible to red squill poisoning while rabbits and chickens are not. It therefore seems that poisoning from red squill is due to a species susceptibility rather than any ability or inability to vomit. It should be noted, of course, that vomiting may protect susceptible animals from red squill poisoning by ridding the animal of the poison.

SUMMARY

1. Chickens and rabbits do not seem to be affected by levels of red squill extract and red squill powder which are definitely toxic to rats. However, rabbits may be susceptible to very high levels of red squill dosage.

2. Guinea pigs are less resistant to poisoning by red squill extract and powder than are rats.

3. It is believed that red squill poisoning is dependent on species susceptibility rather than on ability or inability to vomit.

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On the Preparation of an Extract Having "Marihuana-Like" Activity from the Fruits of Cannabis Sativa

By John R. Matchett and S. Loewe†*

Despite the considerable research carried on in recent years on the separation and characterization of the physiologically active principle or principles of the resin of *Cannabis sativa*, little has been reported concerning the fruits. Munch (1) prepared two physiologically active extracts and found one to be stimulating to mice and the other depressant. Reference to action similar to that of extracts prepared from the vegetative portions of the plant was not made.

Bouquet (2) has examined the fruits and concludes that they themselves are devoid of physiological activity. Any effects observed pursuant to their use he feels must be due to the presence of hulls which do contain resin.

This report records the unequivocal demonstration of the presence in cannabis fruits of a principle or principles having, in the dog, an action similar to that produced by the familiar cannabis resin. The substance or substances are to be found in the non-saponifiable portion of the solvent-extracted oil which is a major constituent of the fruits.

EXPERIMENTAL

The preparation of the active extract was carried out as follows:

Fruits of *Cannabis sativa* (675 Gm.), free from admixed vegetative material, were crushed and extracted to exhaustion with chloroform. Most of the solvent was evaporated at atmospheric pressure and the last traces removed *in vacuo*. The oily

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residue weighed 234 Gm. (33%). This material was dissolved in 750 cc. of 1.25*N* alcoholic potassium hydroxide and the solution was boiled under reflux until saponification was complete. The resulting soap solution was diluted with an equal volume of water and extracted continuously with pentane (Skellysolve *A*) to exhaustion. The pentane solution was washed with water until free from soap, then evaporated on the steam bath. The residue consisted of 4 Gm. (0.6%) of resinous oil in which some crystals were discernible.

The residue was extracted with 35 cc. of alcohol which dissolved most of the material except the crystals and a little resinous matter. The crystals were dissolved in 25 cc. of acetone and the resinous residue in 5 cc. of chloroform. The three solutions were referred to as samples number 1, 2 and 3, respectively.

The crushed fruits remaining in the percolator were extracted to exhaustion with alcohol and the extract concentrated to 250 cc. *in vacuo*. This sample was designated number 4.

The capacity of the preparations to exert a "marihuana-like" action was tested in the dog. When symptoms of motor ataxia (the characteristic effect of cannabis preparations in the dog) were observed in test experiments, the potency of the preparation was evaluated by the procedure of "bioassay by approximation" recently described (3, 4).

The preparations were administered by intravenous injection in a concentrated ethanol or acetone solution, and the intensity of action was recorded in grades (I to VI; according to the scale used by Walton and collaborators (5)).

Sample 2, the ethanol-insoluble, but acetone-soluble fraction from the pentane residue, was found ineffective. This agrees with the experience that in the case of highly potent cannabis tops, under analogous procedures, the active principle is taken up by ethanol extraction and no appreciable amount is left for a subsequent acetone extraction. Accordingly, no activity could be expected in Sample 3 which could not be tested due to its insolubility in any appropriate solvent. Sample 4 was also found ineffective in accordance with the fact that another extract prepared by direct ethanol extraction of defatted seeds was also found devoid of any specific action in the highest dosage which could be administered without non-specific toxic effects.

The main fraction, however, Sample 1, produced varying degrees of ataxia in seven experiments, as shown in Table I. All these experiments were carried out in dogs which had been satisfactorily calibrated with a standard of reference, a highly potent redistillate oil preparation from cannabis tops, before and after the test experiment, and, therefore, the principle of "bioassay by approximation" was applicable to these experiments. Since the application of this assay method to cannabis preparations has hitherto not yet been published *in extenso*, it might be appropriate to exemplify its use in the case of these experiments. This is done in the second part of Table I. This part of the Table enumerates the figures of Maximum and Minimum Potency (3, 4) which were obtained as the ratios between a dose of the standard preparation employed in calibrating the same test dog and the dose of the test preparation, Sample 1. Each ratio obtained under use of a calibration dose which was more effective than the test dose indicates a "Maximum Potency," each ratio with a calibration dose of lower effectiveness than the test dose indicates a "Minimum Potency." These values, grouped in arithmetical progression, as in Table I, show at once the range of potency outlined by the group of experiments; and therefrom a median value of potency can be calculated, as at the bottom of the approximation.

Table I.—Bioassay by Approximation of Non-Saponifiable, Ethanol-Soluble Portion (Sample 1) of Hemp Seeds

Experiments

Experiment No.	Dog No.	Dose in Equivalents of Gm. Seed per Kg.	Intensity of Action
383	9	6.4	IV–V
593	47	5.7	II–III
594	49	5.2	II–III
384	40	4.8	I–II
592	9	3.8	II–III
498	49	3.5	II
554	61	3.2	I
488	49	2.5	II
380	43	1.9	I–II
543	49	0.9	I

Calculation

Experiment No.	Potency of Values in Sequence of Approximation Minimum Potency	Maximum Potency
384	0.040	...
383	0.060	...
594	0.067	...
592	0.100	...
383	0.105	...
380	0.116	...
594	...	0.133
592	...	0.133
593	...	0.137
554	...	0.145
592	...	0.159
380	0.211	...
498	...	0.213
384	...	0.220
592	...	0.228
383	0.232	...
594	...	0.267
380	...	0.291
488	...	0.296
543	...	0.371
383	...	0.416
380	...	0.422
592	...	0.444

Potency = 0.187×10^{-3}.
Range of Deviation: ±33%.

For the sake of convenience, the potency values were multiplied by 10^3 before they were entered into the two last columns of the second part of Table I. The potency value determined in this assay refers to the starting material of Sample 1, *i. e.*, to clean fruits of *Cannabis sativa*, as compared with a potent

redistillate marihuana oil. Considering, accordingly, only the amounts of active principle which were recovered from hemp seeds after saponification of its chloroform extractives, hemp seeds would appear to possess about $^1/_{1000}$ the potency of the marihuana oil employed as standard of reference. This, according to our bio-assays of a great variety of cannabis tops, would signify that hemp seeds were about $^1/_{10}$ to $^1/_{30}$ as potent as the carefully ground and screened parts of dried cultivated tops from various (*e. g.*, Roumanian, Manchurian, Italian) varieties of *Cannabis sativa*, or $^1/_{80}$ to $^1/_{100}$ as potent as herbs from the illegitimate marihuana trade.

CONCLUSIONS

Qualitatively, these experiments give evidence of the presence of an active principle in hemp seeds which is similar in its pharmacological action to that of marihuana oil. Quantitatively, the value of potency found in the present preparation may help to explain why, in quite a number of attempts, we were unable to elicit "marihuana-like" action with less intricately prepared extracts from either total, or crushed, or defatted cannabis fruits, but this potency figure cannot be considered as conclusive with respect to the amount of active principle present in the starting material of our preparation. It is hardly more than a minimum value, and it is open for further investigation to determine how much of the active principle originally contained in the fruits may be lost in preparing this non-saponifiable fraction either by reasons of chemical destruction or due to insufficiencies of the procedures of fractionation.

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"Nothing would be done at all if a man waited till he could do it so well that no one could find fault with it."—John Henry Newman.

Alkyl Nitrites. VII

Synthesis of Some Organic Nitrites and Nitrates*

By Sylvan E. Forman, C. Jelleff Carr and John C. Krantz, Jr.

In the course of certain studies on the pharmacology of nitrites (1, 2, 3) and nitrates (4, 5), it was necessary to synthesize a number of organic compounds. We are reporting in this paper the data accumulated on the chemistry of these substances.

The nitrites were prepared from the corresponding alcohols and nitrous acid in the same manner as described for the preparation of 2-ethyl-*n*-hexyl-1-nitrite. Myristyl, cetyl and *n*-octadecyl alcohols were dissolved in diethyl ether before they were treated with nitrous acid. Nitrite nitrogen was determined in these compounds by the nitrometer method described for the assay of amyl nitrite in the U. S. Pharmacopœia X, page 49. In the analysis of myristyl, cetyl and octadecyl nitrites, the aqueous potassium iodide solution had to be replaced with potassium iodide solutions in 75 per cent ethanol, because of the greater insolubility of these nitrites in water.

Propyl, butyl and heptyl glycollates were prepared by fractionating mixtures of glycollic acid, benzene and a little sulfuric acid with an excess of the corresponding alcohol as in the description of the preparation of the propyl ester.

The nitrates were prepared in the manner described for the preparation of isoamyl lactate nitrate. In some cases it was necessary to pour the nitrating mixtures into ice water to obtain the product. These compounds were analyzed by the well-known modification of the Kjeldahl method which employs salicylic acid and sodium thiosulfate to reduce the nitrates.

In addition to the compounds listed in the experimental portion, the following were also prepared but the analyses indicated that they were not obtained pure: *n*-nonyl-

* Contribution from the Department of Pharmacology, School of Medicine, University of Maryland.

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1-nitrite, b. p. 63° C./2 mm.; 5-ethyl-*n*-nonyl-2-nitrite, b. p. 67° C./2 mm.; lauryl nitrite, b. p. 90° C./2 mm.; 7-ethyl-2-methyl-*n*-hendecyl-4-nitrite, b. p. 87° C./2 mm.; myristyl nitrite, b. p. 110° C./1 mm.; cetyl nitrite; heptyl glycollate nitrate, b. p. 146° C./17 mm.; glycerin 1, 3 diacetate-2-nitrate; pinite nitrate; adonitol pentanitrate; polygalitol tetranitrate; sorbitan tetranitrate. All of these compounds were liquids, but the last four were syrups.

EXPERIMENTAL

2-Ethyl-n-hexyl-1-nitrite.—One hundred and forty-three Gm. of 2-ethyl-hexan-1-ol were poured over 220 ml. of 6*N* hydrochloric acid and the mixture was cooled to 0° C. One hundred and ten Gm. of sodium nitrite in 550 ml. of water were added with stirring. The aqueous layer was separated from the upper layer which was dried with magnesium sulfate. The liquid distilled at 63° C./19 mm. The yield was 159 Gm. (91%), specific gravity $\frac{22°}{23°}$ C. 0.878./ml. in air. *Analysis.*—Calcd for $C_8H_{17}NO_2$: N, 8.80. Found: N, 8.69.

n-Octadecyl Nitrite.—The liquid was distilled at a pressure below 1 mm. between 138° and 144°. *Analysis.*—Calcd. for $C_{18}H_{37}NO_2$: N 4.68. Found: N, 4.61, 4.66.

Isoamyl Lactate.—This compound has been synthesized by refluxing anhydrous lactic acid with isoamyl alcohol in the presence of sulfuric acid (6).

The material used in this research was prepared in the following manner: One mol of 85% lactic acid and 1 mol of isoamyl alcohol were mixed and saturated with dry hydrogen chloride. After three hours, the mixture was poured into water. The upper layer was separated and washed, first with water and then with sodium bicarbonate solution. The liquid was dried with magnesium sulfate. The fraction which distilled 96–100° C./23 mm. weighed 40 Gm. (25%).

Propyl Glycollate.—Schreiner first synthesized this compound from propyl chloroacetate and sodium glycollate (7).

The authors prepared it as follows: 76 Gm. of glycollic acid, 225 Gm. of *n*-propanol, 500 ml. of benzene and 2.5 ml. of concentrated sulfuric acid were mixed and fractionated slowly. About 500 ml. of the distillate were collected in 5 hours. The acid was neutralized with 10 Gm. of calcium carbonate and the liquid was fractionated. The material which distilled 74–75° C./20.5–21.5 mm. weighed 85 Gm. (71%).

Butyl Glycollate.—The yield from one mol of glycollic acid was 108.5 Gm. (81%) which distilled 87–88° C./20.5 mm.

Heptyl Glycollate.—The yield from 0.55 mol of glycollic acid was 57 Gm. (60%) which distilled 125–130° C./16–17 mm.

Isoamyl Lactate Nitrate.—Forty Gm. of isoamyl lactate were dissolved in 35 ml. of nitric acid (sp. gr. 1.5) which was kept cold in an ice bath. Fifty-five ml. of concentrated sulfuric acid were added slowly with stirring to prevent an excessive rise in temperature. The upper layer was separated from the acid and washed twice with water and once with sodium bicarbonate solution. The yield was dried with magnesium sulfate and fractionated. The material which distilled at 70° C./1 mm. weighed 33 Gm. (65%). *Analysis.*—Calcd. for $C_5H_{10}NO_3$: N, 6.83. Found: N, 6.78, 6.73.

Propyl Glycollate Nitrate.—Forty-eight Gm. of propyl glycollate yielded 43 Gm. (65%) of the nitrate which distilled 94–96° C./18.5–20 mm. *Analysis.*—Calcd. for $C_5H_9NO_5$: N, 8.59. Found: N, 8.30, 8.29, 8.40.

Butyl Glycollate Nitrate.—Thirty-nine Gm. of butyl glycollate yielded 37 Gm. (73%) of the nitrate which distilled 109.5–110° C./19–19.5 mm. *Analysis.*—Calcd. for $C_6H_{11}NO_5$: N, 7.91 Found: N, 7 74, 7.76, 7.83

Isomannide Dinitrate.—Fifty Gm. of isomannide yielded 45 Gm. (55%) of nitrate. The product was recrystallized from 95 per cent ethyl alcohol until it melted constantly at 65.5° C. *Analysis.*—Calcd. for $C_6H_8N_2O_8$: N, 11.86; C, 30.52; H, 3.41. Found: N, 11.54, 11.55; C, 30.44, 30.65; H, 3.45, 3.38.

Isosorbide Dinitrate.—Isosorbide dinitrate was prepared from the dianhydride of sorbitol which was prepared by dehydration of sorbitol with metaphosphoric acid in a manner analogous to the preparation of isomannide from mannitol.

Twenty Gm. of isosorbide yielded 27 Gm. (83%) of nearly pure nitrate, m. p. 50–51° C. One recrystallization from 95 per cent ethyl alcohol raised the melting point to 52° C. *Analysis.*—Calcd. for $C_6H_8N_2O_8$: N, 11.86; C, 30.52; H, 3.41. Found: N, 11.58, 11.48; C, 30.72; H, 3.44.

Erythritan Dinitrate.—Eighteen Gm. erythritan yielded 15 Gm. (45%) of nitrate which distilled 89°/1 mm. *Analysis.*—Calcd. for $C_4H_6N_2O_7$: N, 14.43. Found: N, 14.08, 14.11.

SUMMARY

The foregoing compounds, some of which are of therapeutic interest, have been synthesized.

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A Sterol from Apple Seeds and Cherry Seeds

*By Harold M. Sell and Roland E. Kremers**

In addition to reporting some physical constants of apple seed oil, Pritzker and Jungkunz (1) mention a phytosterol acetate, melting point 122° C., which they obtained from this oil. A search of the literature, however, disclosed no report of the identification of a sterol from either apple seeds or cherry seeds (2, 3). This paper not only reports some constants of the oil extracted from these seeds, but also describes the isolation of a sterol from this oil and its characterization as sitosterol.

EXPERIMENTAL

Isolation of Sitosterol from Apple Seeds.—The apple seeds used were obtained from dried apple pomace.[1] The seeds were separated by screening, washed with water, dried and then ground in a Wiley mill. Extraction for 20 hours with Skellysolve *B* was carried out in a continuous extractor charged with 1150 Gm. of the ground material. The solvent was removed by distillation under reduced pressure and the acid number, saponification number and refractive index of the oily residue were determined (Table I).

Saponification of 200 Gm. of this oil was carried out by refluxing for 6 hours with 400 ml. of 5% alcoholic potassium hydroxide. After dilution with 400 ml. of water, the solution was extracted with Skellysolve *B*. Washing with water freed the extract of soaps. Removal of the solvent by distillation under diminished pressure yielded the unsaponifiable fraction as 3.5 Gm. of a noncrystalline residue.

This unsaponifiable fraction was taken up in ethyl alcohol and treated with a 200 cc. of a 1% digitonin solution (4). The sterol digitonide was collected upon a Büchner funnel and washed thoroughly, first with hot chloroform, then with ether. The dried residue was acetylated (5) by refluxing for one hour with acetic anhydride. Upon cooling, the sterol acetate separated as crystals. This crystalline material was collected upon a Büchner funnel, then recrystallized from acetic anhydride. A portion of the acetate was saponified by refluxing for 5 hours with 40 ml. of 5% alcoholic potassium hydroxide. The sterol, which separated as crystals upon cooling the saponification mix, was repeatedly recrystallized from absolute methanol until a constant melting point was obtained. Both the sterol and the sterol acetate were finally dried for one hour in an Abderhalden drier at 110° C. and 4 [illegible] mm. pressure.

Isolation of Sitosterol from Cherry Seeds.—Red cherries, collected locally during the month of July, were used. The seeds were expressed from the fruit, sorted from injured seeds and dried. The procedure for isolation and characterization of the sterol was the same as that used in the case of apple seeds. Collected data are given in Tables I and II. It is evident that the same sterol exists in the seeds of both the apple and the red cherry.

Table I

	Apple		Cherry
	Literature (1)	Determined	
Per cent of oil in seeds	18.0	19.1	8.2
Acid number of oil	2.3	0.9	0.8
Saponification number of oil	187.7	186	189
n_D^{21}	...	1.4735	1.4744
Per cent unsaponifiables obtained	1.10	1.75	4.15

Table II

	Apple		Cherry
	Literature (1)	Determined	
Melting point of sterol acetate, ° C.	122	123	121
α_D^{31} of sterol acetate	...	−35.4	−34.8
Melting point of sterol, ° C.	...	137–138	137–138
Liebermann - Burchard Test	...	+	+
Whitby's Salkowski Test	...	+	+
Whitby's Test B	...	+	+

SUMMARY

1. Sitosterol has been isolated from both apple and red cherry seeds.

2. The refractive index, acid number and saponification number of both apple and cherry seed oil are reported.

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[1] We are indebted to Mr. L. A. Pridgeon of the Certo Division, General Foods Corporation, for supplying us with 2 Kg. of dried apple seeds.

A Review of Tests for Ephedrine*

By Margaret Elverston and Edward S. Brady, II

EPHEDRINE

The medicinal properties of the Chinese plant Ma Huang were discovered nearly five centuries ago, but it was not until the latter part of the nineteenth century that its active principle, ephedrine, was isolated by Nagai (1887) and Merck (1888). It was re-isolated in 1923 by Chen and Schmidt (1) and, after extensive research, was recognized and admitted to the British Pharmacopœia, the Chinese Pharmacopœia and the United States Pharmacopœia. Ephedrine was synthesized by Nagai and Kano in 1929; previously (1921) Spath had investigated a synthetic product and had shown it to be identical with the natural alkaloid (2). Other syntheses have been more recently studied and developed.

Structure.—Chemically the ephedrine base is $C_{10}H_{15}ON$, β-phenyl-β-hydroxy-α-methyl-ethyl-methylamine or α-hydroxy-β-methyl-aminopropyl-benzene. There are 2 *a*-symmetric carbon atoms which give rise to six stereoisomers, *d*-, *l*- and *dl*-ephedrine and *d*-, *l*- and *dl*-pseudo-ephedrine (3). The laevo form is the one official in the United States Pharmacopœia as the free alkaloid, the hydrochloride and the sulfate. The commercial title "Ephetonin" is applied to the racemic form, as the hydrochloride. Synthetic products which have a structure similar to that of ephedrine include Synephrine, Neo-synephrin, Benzedrine, Propadrine, Veritol, Suprifen, Cobefrin and Isalon (3).

Sources.—The varied sources of the first ephedrine samples and the introduction of the various synthetics under similar names have caused some confusion to the analyst. The present chief natural source, *Ephedra Sinica*, contains some seven closely related bases, in addition to ephedrine base, which may exist as *d*, *l* and racemic forms (3, 4, 11). The synthetic ephedrines first introduced were often mixtures of various proportions of *d*- and *l*- ephedrine. Thus the task of establishing identity tests for ephedrine, already difficult because of the chemical nature of the drug, became still more involved due to the lack of uniformity of samples to be tested. Even in recent literature there seems to be some confusion in nomenclature and tests, and it is the purpose of this paper to review and to attempt to clarify the tests for the identification of *l*-ephedrine and its salts.

Physical Tests.—Ephedrine (base) United States Pharmacopœia, Eleventh Revision, is described as an unctuous, almost colorless solid, or white to colorless crystals or granules. It is soluble in water, alcohol, ether, chloroform and liquid petrolatum, insoluble in petroleum ether. It is alkaline to litmus. Ephedrine hydrochloride and sulfate are described as fine, white, odorless crystals or powder. The rather wide range given for the melting points, particularly of the base, is due to the variation in moisture content. The sulfate is soluble in water and hot alcohol, more difficulty soluble in cold alcohol, while the hydrochloride is soluble in water and alcohol and insoluble in ether. Physical constants of ephedrine and its salts are tabulated in the chart below.

* From the Department of Pharmaceutical Chemistry, College of Pharmacy, University of Southern California, Los Angeles, California.

Table I.—Physical Constants of Ephedrine and Its Salts

Form	Melting Point, °C.	Boiling Point, °C.	Specific Rotation	Source of Data
Base	34 to 40		As HCl, 0.5 Gm./10 cc. −33.0° to −35.5°	U. S. P. XI (7)
Base	38.1	225	−6.3° (3.5% in EtOH) +11.2° (in water)	Henry (5)
Base	43	225	−5.08° (3% in EtOH) +14.95° (2% in water)	Rosenthaler (6)
HCl	216 to 220		−33.0° to −35.5°	U. S. P. XI (7)
SO_4	240 to 247.5°		−29.5° to −32°	U. S. P. XI (7)

[a] Omitted in the Second Supplement to the U. S. P. XI.

Moore and Tabern have made a thorough investigation of the melting points and solidification temperatures of ephedrine (8). Standards of ephedrine based on total alkalinity, specific rotation and congealing point have been adopted by the American Drug Manufacturer's Association (9).

Macrochemical Tests.—Derivatives of ephedrine are formed in most of the accepted analytical organic reactions. Heated with iodine in an alkaline medium (sodium hydroxide), iodoform is obtained. This reaction is the basis for a quantitative estimation. Benzoic acid may be obtained by oxidizing ephedrine in an alkaline hydroxide solution; distillation of ephedrine with potassium permanganate yields benzaldehyde and fatty amines (10). The odor of benzaldehyde was observed upon the mixing of a drop of 0.1% ephedrine solution with a drop of 10% potassium permanganate solution on a microscope slide, even without heating. Nitrosoephedrine is formed when ephedrine is allowed to react with sodium nitrite and hydrochloric acid. A diazo compound is formed upon nitration and subsequent reaction with zinc and sodium nitrite (10). Ephedrine may be converted into its stereoisomeride pseudo-ephedrine by boiling with 25% hydrochloric acid. This reaction is reversible, an equilibrium mixture of the two bases being formed in each case. Acylation produces the same result (5). Unlike other alkaloids, ephedrine base in chloroformic solution reacts to form the hydrochloride, which is the basis for a U. S. P. XI test, as follows: "Dissolve 0.05 Gm. of Ephedrine in 10 cc. of chloroform, allow the solution to stand over night in a closely covered vessel, and then evaporate it spontaneously: white crystals of ephedrine hydrochloride appear, which, when dissolved in water, respond to the identity tests for chloride."

Color Tests.—Color tests are the most generally used tests for the identification of ephedrine.

The U. S. P. XI test is as follows: "Dissolve 0.01 Gm. Ephedrine in 1 cc. distilled water with the aid of 1 or 2 drops of dilute hydrochloric acid and add 0.1 cc. of cupric sulfate T. S. followed by 1 cc. of sodium hydroxide solution (1 in 5): a reddish purple color develops. To the mixture add 1 cc. of ether and shake well: the ethereal layer is purple and the aqueous layer is blue." A study of this reaction with ephedrine and nineteen homologs was made by K. K. Chen (11).

In the Dènigés test, ephedrine is dissolved in 2 cc. of concentrated sulfuric acid (to a colorless solution), and three or four drops of a 40% formaldehyde solution are added. A pink color develops which darkens to red and finally to blood-red when heated on a water bath (16). Boil 0.01–2 Gm. ephedrine with 1 cc. of a mixture of equal parts of nitric and sulfuric acid until brown, add 10 cc. of water and sodium hydroxide until neutral (red color); extract with ether and evaporate this solution (cool); add 2 cc. acetone and 2 cc. sodium hydroxide (33° B.). The acetone layer will be red, the sodium hydroxide yellow (12).

The bromalid reaction yields a pink to red color in the upper layer of a mixture prepared by dissolving 0.1 Gm. ephedrine in 3 cc. of water, adding five drops of sodium hypobromite solution, then 1 cc. of sodium hydroxide (d. 1.33), 1 to 2 cc. pyridine and shaking. The red color appears in the upper layer upon heating (12).

Selenious acid in sulfuric acid with ephedrine yields an olive to red color. This reaction may be used to differentiate ephedrine from adrenaline, since adrenaline forms a red color with this reagent only upon heating. A further test for differentiation is the lack of any color change in an ephedrine solution upon the addition of sulfanilic acid and sodium nitrite, even when heated; adrenaline yields a rose color with these reagents (13).

A few drops of osmium tetraoxide reagent (3 cc. of 1% aqueous solution osmic tetraoxide and 2 drops of sodium hydroxide 36° B.) added to a crystal of *l*-ephedrine (base or hydrochloride) dissolved in 1 cc. of water forms an orange-colored precipitate instantly; if a small amount of this precipitate is heated with 5 cc. of pure hydrochloric acid a violet color is rapidly obtained. Performance of this test with the pseudo-ephedrines and their salts results in the slow

formation of a yellow precipitate which dissolves without change in hydrochloric acid to form a yellow solution (14).

Microchemical Tests.—Investigation of the reactions of ephedrine with the various alkaloidal precipitants began with widespread acceptance of ephedrine by the medical profession. Results were not entirely satisfactory, since ephedrine is slow to form crystalline precipitates and long standing is necessary in most cases. Thus the concentration of the drops vary greatly from test to test because of evaporation, depending upon temperature and surface of the drop. The results of a critical laboratory survey of these microchemical tests is here presented.

EXPERIMENTAL

Materials Used: Ephedrine hydrochloride, Parke, Davis & Co., ephedrine base, solutions of reagents as stated under each test. Most of the tests were performed using 1% solutions of the alkaloidal salt. When too large a volume of precipitate was formed at that concentration, the solutions were diluted to strengths varying from 0.5% to 0.10%. In less sensitive tests, successive drops of the 1% solution were evaporated upon the microscopic slide until a concentration of the alkaloid was obtained which gave a good test.

Technique.—The simple technique consists of placing a drop of the alkaloidal solution upon one end of a clean glass plate slide by means of a glass rod or dropper and spreading it slightly. The reagent, if liquid, is placed next to the alkaloidal drop in the same manner, not quite touching it, and the two are joined by drawing a platinum or glass capillary rod across the reagent drop and allowing it to flow into the alkaloidal drop (6). This produces zones of varied relative concentrations of alkaloid and reagent throughout the drop and provides some optimum zone where crystallization will be best. Where two or more drops are added to a test drop, the ones which cause no precipitation may be first mixed directly with the test drop. Solid reagents are added to the edge of the drop by means of a capillary glass rod or platinum wire. The solid may be made to adhere to the rod by breathing upon the rod or by dipping it in distilled water and shaking off the excess. No cover slip is used and the drop is examined through the microscope under low power magnification, 100×.

Gold Chloride.—Yellow oily droplets are at first observed upon the addition of gold chloride (1% aqueous solution) to a test drop containing ephedrine. Needles and blades are formed slowly upon standing, but in dilute drops these may be confused with reagent deposited through evaporation of the test drop. Though reported by many observers (15, 16), this test did not appear to be very reliable.

Platinic Chloride.—Pale yellow silky needles slowly appear at the periphery of the drop containing ephedrine upon standing after the addition of 1% platinic chloride solution. This is quite sensitive (1:10,000) but forms slowly (15) (Fig. 1).

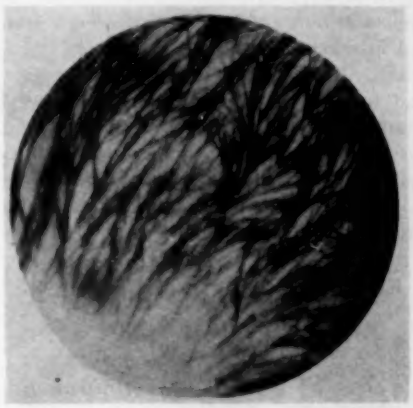

Fig. 1.—Ephedrine with Platinic Chloride T.S.

Krauts or Dragendorff's Reagent (*Potassium Bismuth Iodide*).—This reagent seems to present the best means for the micro-identification of ephedrine. Groups of red-brown branching needles and blades form rather rapidly upon the addition of this reagent (Fig. 2). This test was adopted by the Association of Official Agricultural Chemists (17). Ephetonin forms similar crystals (6); amorphous precipitates only were obtained by other observers (16).

Fig. 2.—Ephedrine with Dragendorff's Reagent.

Potassium Iodide repeatedly failed to yield any but reagent crystals in test drop to which it was added. Rhombs and prisms previously reported

(16) seemed to form with equal rapidity in all test drops, whether or not they contained ephedrine, due to crystallization of the reagent.

Picric Acid.—Yellow oily droplets formed upon the addition of a 1% aqueous solution of picric acid to a test drop containing ephedrine remain unchanged for so long a period (often 15 minutes) that a negative test has been reported in some instances (12). However, brown mossy growths which formed rosettes and burrs of light brown needles were observed in many concentrated test drops upon long standing. This crystalline growth is unlike any crystal formed by picric acid alone upon partial spontaneous evaporation of a test drop, and was successfully used to aid the more rapid formation of crystals in other ephedrine drops through seeding (Fig. 3). Ephetonin forms branching rods with this reagent (6).

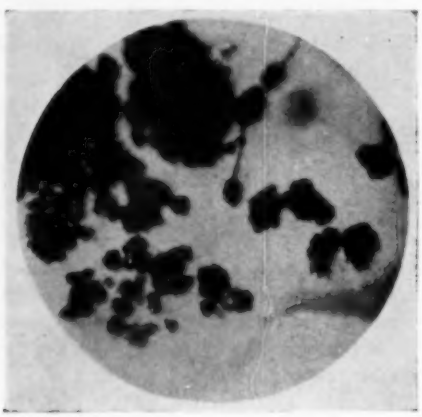

Fig. 3.—Ephedrine with Picric Acid T.S.

Potassium Thiocyanate.—Large irregular plates and prisms were formed upon the addition of potassium thiocyanate to an ephedrine test drop (Fig. 4). This has been reported by other observers (16), and may be used to differentiate ephedrine from ephetonin, which forms rectangular plates (6).

Fig. 4.—Ephedrine with Potassium Thiocyanate T.S.

Potassium Oxalate.—A small crystal of potassium oxalate placed at the edge of a test drop containing ephedrine hydrochloride forms straight light needles or prisms, singly and in groups (Fig. 5). Ephetonin forms thin rhombic coalescent crystals (18).

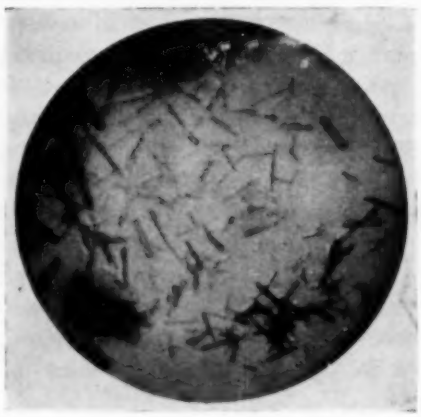

Fig. 5.—Ephedrine with Potassium Oxalate T.S.

Sodium Perchlorate.—Rectangular plates were formed when a fragment of this salt was added to an ephedrine test drop (Fig. 6) (6).

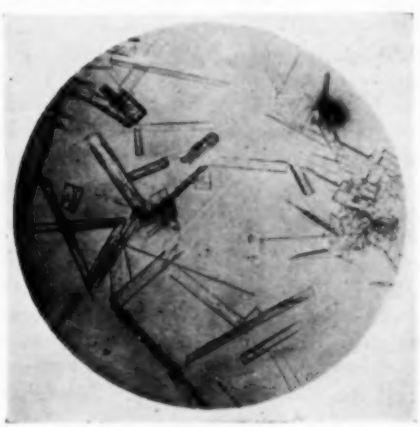

Fig. 6.—Ephedrine with Sodium Perchlorate T.S.

Sodium Vanadate produced with ephedrine a white granular precipitate only; ephetonin is reported to form spindle-shaped crystals and conglomerates with this reagent (18).

Salting Out.—Crystal formation due to salting out was suspected at the high concentrations required by some tests, but the addition of excess calcium chloride to a test drop of ephedrine hydrochloride formed irregular plates and blades, somewhat like those formed with potassium thiocyanate, but unlike others (Fig. 7). Amorphous precipitates are formed with Mayer's Reagent, Wagner's Reagent and phosphomolybdic acid; no tests were obtained with mercuric chloride, sodium nitroprusside, bismuth nitrate, ammonium molybdate, phospho-

Fig. 7.—Ephedrine Salted out with Sodium Chloride.

tungstic acid and zinc-chlor-iodide. A nitrous acid tests was not successful, probably due to rapid dissipation of the acid at room temperature. Million's reagent, also reported as a precipitating reagent (15), formed clear solutions with samples tested, no crystalline precipitate being obtained even on long standing. The orange precipitate of the osmic acid color test (14) was examined microscopically but appeared to consist entirely of amorphous masses.

SUMMARY AND CONCLUSION

The authors have presented a review and discussion of tests for *l*-ephedrine and its salts and a laboratory survey of microchemical tests for this alkaloid, from which the following conclusions may be drawn:

1. Numerous acceptable tests for ephedrine have already been devised. Of these, the color and microscopic methods seem to offer the best means of identification.

2. The U. S. P. XI biuret reaction and the osmic tetraoxide reagent seem to give the best color tests.

3. Microcrystalline precipitates form slowly in ephedrine test drops, but identification may be made through the micro tests with Dragendorff's Reagent, platinic chloride reagent and potassium oxalate.

4. A combination of these tests may be used to distinguish *l*-ephedrine from ephetonin, the pseudo-ephedrine and adrenaline.

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A Study of the Composition of Precipitated Calcium Phosphate National Formulary VI*

By J. W. Millar

The formula given in National Formulary VI for Precipitated Calcium Phosphate is $Ca_3(PO_4)_2$ and the same formula is given in the French Codex for "Neutral Calcium Phosphate." The British Pharmacopœia gives no formula, but Bennett and Cocking (1) attribute the following formula to the salt of the British Pharmacopœia:

$$CaH_4(PO_4)_2 + 2[3Ca_3(PO_4)_2.Ca(OH)_2]$$

* Contribution from the Laboratories of the College of Pharmacy, University of California, Medical Center, San Francisco, California.

The salt is not official in the German Pharmacopœia.

Mellor (2) and others (3) apparently doubt the correctness of the formula given in N. F. VI, Mellor stating that "Strictly normal Calcium Phosphate has not been prepared in the wet way."

The equation of formation of the salt where shown in texts (4) is:

$$3CaCl_2 + 2Na_2HPO_4 + 2NH_4OH = Ca_3(PO_4)_2 + 4NaCl + 2NH_4Cl + 2H_2O$$

The formula given in the National Formulary VI, namely, $Ca_3(PO_4)_2$ with a molecular weight of 310.28, gives a theoretical composition: Ca 38.75 per cent and PO_4 61.24 per cent. These results were not obtained in any of the analyses carried out in this laboratory, the results for calcium being invariably higher and for phosphate lower than the above theoretical values.

The formula given by Bennett and Cocking (1), $CaH_4(PO_4)_2 + 2[3Ca_3(PO_4)_2.Ca(OH)_2]$, gives a theoretical composition: 38.09 per cent, PO_4 60.19 per cent, and shows the presence of 10.59 per cent of mono-calcium-ortho phosphate, $CaH_4(PO_4)_2$, a soluble salt.

From the analysis carried out in this laboratory, the possibility of a basic salt became apparent and the following formula is suggested:

$[Ca_3(PO_4)_2]_3$. $Ca(OH)_2$, mol. wt. 1012.14

which has the following theoretical composition:

Ca	40.31 per cent
PO_4	56.33 per cent
$(OH)_2$	3.37 per cent

or calcium combined with

PO_4	35.88 per cent
PO_4	56.73 per cent
$Ca(OH)_2$	7.37 per cent

An equation for the formation of a basic salt may be shown as:

$$10CaCl_2 + 6Na_2HPO_4 + 8NH_4HO = [Ca_3(PO_4)_2]_3.Ca(OH)_2 + 12NaCl + 8NH_4Cl + 6H_2O$$

This basic salt may be converted at high temperature to $[Ca_3(PO_4)_2]_3$. CAO giving a theoretical composition of:

Ca	40.31 per cent
PO_4	56.33 per cent
O (combined as CaO)	1.57 per cent
	98.21 per cent
Water (due to conversion of $Ca(OH)_2$ to CaO)	1.78 per cent
	99.99 per cent

EXPERIMENTAL

All samples of the salt analyzed conformed with the tests for purity listed in N. F. VI; and no appreciable residue was obtained when the salt was well shaken with water and the filtrate evaporated to dryness.

The two samples used for analysis were obtained from commercial sources; number one labeled "Calcium Phosphate—Tribasic—Precipitated P-W-R," number 2 labeled "Calcium Phosphate Merck—Tribasic—Precipitated."

Table I.—Comparison of Results Found with Those Computed

	N. F. VI $Ca_3(PO_4)_2$ M. W. 310.28	B. & C. (1) $CaH_4PO_4 + [2\,3Ca_3(PO_4)_2.Ca(OH)_2]$ M. W. 2209.96	Suggested $[Ca_3(PO_4)_2]_3.Ca(OH)_2$ M. W. 1012.14	Results Obtained, Average
Ca	38.75	38.09	40.31	40.12
PO_4	61.24	60.19	56.33	56.43
O (calculated)	...	0.72	1.57	1.57
H_2O from $Ca(OH)_2$ on ignition	...	0.81	1.78	1.83
H in $CaH_4(PO_4)_2$	...	0.18	...	...
Total	99.99	99.99	99.99	99.95

Samples were dried at 200° C. to constant weight.

The analytical method used for phosphorus was: precipitation as ammonium phospho-molybdate; the precipitate dissolved in ammonia; phosphate precipitated with magnesia mixture. Weighed as magnesium pyro-phosphate (5). The calcium was precipitated as oxalate with ammonium oxalate and converted to calcium carbonate by careful ignition at 500° C. (±10° C.).

The monograph in National Formulary VI states that, "When dried to constant weight at 200° C., the salt loses not more than 4 per cent in weight (water)."

Pure calcium phosphate is unaffected by heat up to 1670° C. (6). Calcium hydroxide loses water at 580° C.

The samples analyzed lost (av.) 3.76 per cent in weight when heated at 200° C. to constant weight; and at a temperature of 1500° C. for two hours lost a further 1.83 per cent, apparently not due to hygroscopic moisture.

SUMMARY

From the analytical results obtained it appears that the formula for precipitated calcium phosphate, $Ca_3(PO_4)_2$, given in the National Formulary VI and in the French Codex are in error.

It also appears that the formula suggested $[Ca_3(PO_4)_2]_3.Ca(OH)_2$ more closely agrees with the true composition of the salt.

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Pharmaceutical Emulsions. III. A Comparative Study of Various Mechanical Stirrers and the Hand Homogenizer*,†

*By William J. Husa‡ and Charles H. Becker***

INTRODUCTION

In earlier papers (1, 2) detailed studies were made of the Continental and English methods of emulsification. The present investigation is devoted to a study of the efficiency of these older methods of emulsification as compared with the use of mechanical stirrers and a homogenizer for making emulsions.

EXPERIMENTAL

Materials.—The stirrers used were: (*a*) motor stirrer, with a glass stirring rod, maximum speed about 3000 r. p. m., purchased from the Central Scientific Co., (*b*) Arnold automatic mixer, intended for use at the soda fountain, (*c*) hand egg beater. A portable hand homogenizer, purchased from the International Emulsifiers, Inc., was employed.

The fixed oils chosen for study were linseed oil, cod liver oil, heavy mineral oil and castor oil. All the oils were of U. S. P. grade. Powdered acacia, U. S. P., was employed. One-tenth per cent sodium benzoate was added to the distilled water to prevent mold growth in the emulsions while standing for observation. *Methods.*—The general methods employed were the same as described in previous papers (1, 2).

Throughout, the parts of acacia were measured in Gm. and the parts of oil and water were measured in cc.

In the tables "oil sep." is used to indicate oil separation. The following abbreviations are used to indicate the average size of the oil globules:

A—Average diameter less than 2.5 microns.
B—Average diameter from 2.5 to 4 microns.
C—Average diameter from 4 to 6 microns.
D—Average diameter more than 6 microns.

Use of Motor Stirrer.—Four-ounce portions of 12½% oil emulsions were prepared using the 4:2:1 proportion. In all cases the stirring was conducted at maximum speed. The emulsions were prepared in the following ways:

Method I: The 4 parts of oil and 1 part of acacia were first mixed well in a 150-cc. beaker with the motor stirrer, and then the 2 parts of water was added all at once. The primary emulsion was stirred for 5 minutes, and the remainder of the water was added gradually.

Method II: The primary emulsion was first made using a porcelain pestle, 15.0 cm. in length and 4.5 cm. in diameter at the base, and a No. 1 wedgwood mortar, and then this was transferred to a 150-cc. beaker and stirred for 5 minutes. The remainder of the water was added gradually.

Mineral oil did not yield an emulsion when made according to the procedure described in Method I. With cod liver oil and linseed oil, the motor stirrer appeared to be of little value, inasmuch as 5 minutes of stirring yielded emulsions which were equivalent, with respect to the average size of the oil globules, to products wherein the primary emulsion was triturated in a mortar for 1 minute. Castor oil yielded a Grade *A* emulsion.

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* Presented before the Scientific Section, A. PH. A., Richmond meeting, 1940.

† This paper is based on part of a thesis presented to the Graduate Council of the University of Florida in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

‡ Head Professor of Pharmacy, University of Florida.

** Graduate Scholar, University of Florida, 1939–1940.

When making emulsions as described in Method II, similar results were obtained. Castor oil yielded a Grade *A* product, whereas the other oils yielded emulsions which were inferior to those made by longer trituration in a mortar.

Stirring the primary emulsions in a 4-ounce-square powder jar was of no advantage.

Use of Hand Egg Beater.—Six-ounce portions of 12½% oil emulsions were prepared using the 4:2:1 proportion and employing a No. 3 wedgwood pestle and a No. 3 wedgwood mortar. The 4 parts of oil and 1 part of acacia were first triturated well, and then the 2 parts of water was added all at once. The resulting primary emulsion was triturated with the pestle for about a half minute, after which the hand egg beater was used to stir the primary emulsion for 5 minutes. The remainder of the water was added gradually, triturating constantly with the pestle.

With respect to stability and the average size of the oil globules, stirring of the primary emulsion with a hand egg beater produced emulsions equal to those in which the primary emulsion was triturated with a pestle for 5 minutes.

Use of Arnold Automatic Mixer.—Sixteen-ounce portions of 25% oil emulsions were prepared using the 4:2:1 proportion. When using the Continental method of emulsification, the 4 parts of oil and 1 part of acacia were stirred well in the Arnold automatic mixer, and then the 2 parts of water was added all at once. The resulting mixture was stirred for 5 minutes and then the remainder of the water was added slowly. When employing the English method, the acacia and water were first made into a mucilage and placed in the mixer. The oil was added gradually, allowing the oil to be well emulsified before the next portion was added. After adding the total amount of oil, the mixture was stirred for 5 minutes and then the remainder of the water was added gradually. The results of use of the Arnold automatic mixer are given in Table I.

Table I.—Use of Arnold Automatic Mixer

Oil	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules
	Continental Method	
Cod liver oil	No emulsion formed	
Linseed oil	No emulsion formed	
Mineral oil	Stable	*A*
Castor oil	Stable	*A*
	English Method	
Cod liver oil	Stable	*A*
Linseed oil	Oil sep.	*A*
Mineral oil	Stable	*A*
Castor oil	Stable	*A*

Results of Table I show that in the case of the Continental method, an emulsion could not be formed with cod liver oil and linseed oil; mineral oil and castor oil yielded Grade *A* emulsions. When using the English method, only linseed oil yielded a poor emulsion which showed oil separation within a period of 3 hours of standing.

When making 8-ounce portions of 50% oil emulsions using the Continental method in the Arnold automatic mixer, it was also found that mineral oil and castor oil yielded Grade *A* products, whereas no emulsions could be formed with linseed oil and cod liver oil.

Use of Hand Homogenizer.—Although it is generally accepted that a homogenizer will reduce the size of the oil globules in an emulsion prepared with a mortar and pestle, yet, little comparative study has been made on this phase with respect to emulsions prepared with various fixed oils. Sixty cc. portions of 12½% oil emulsions were prepared using various proportions of acacia and employing a No. 1 wedgwood pestle and a No. 1 wedgwood mortar. The 4 parts of oil and acacia were triturated well and the 2 parts of water was added all at once. Where a primary emulsion resulted, it was triturated for about a half minute, and then the remainder of the water was added gradually. In cases where a primary emulsion did not form, the remainder of the water was added, nevertheless, to make up to volume. In all cases, the final product was passed three times through a hand homogenizer. The results of the use of a hand homogenizer are given in Table II.

Results on homogenization of the various fixed oils show that in the case of linseed oil and cod liver oil Grade *A* preparations were formed when using from 4 parts to 0.013 part of acacia. The linseed oil emulsions showed creaming within a period of 3 hours. In the case of castor oil and mineral oil the hand homogenizer did not seem to have much advantage over the mortar and pestle method of making emulsions. Although the homogenizer permitted emulsification with lower proportions of acacia, more stable emulsions were produced with the mortar and pestle method when using one or more parts of acacia for 4 parts of oil.

It was noticed that passing an emulsion more than 3 times through the homogenizer did not seem to cause further reduction in the size of the oil globules.

When making 50% oil emulsions with the use of the hand homogenizer, similar results were obtained except that the finished products were found to show less creaming within a 3-hour period of standing.

Castor oil has an unusually high viscosity. Heat tends to lower surface tension. A 60 cc. portion of a 12½% castor oil emulsion was prepared using the 4:2:1 proportion and triturating the primary emulsion for 1 minute. The finished product was heated to 35° C. and then passed three times through the hand homogenizer. Heating the emulsion to 35° C. was of no advantage since it did not cause further reduction of the oil globules when passed through the homogenizer.

Four ounces each of homogenized cod liver and linseed oil emulsions containing 0.05 part of acacia

Table II.—Use of Homogenizer

Parts of Acacia[a]	*Linseed Oil* Appearance of Emulsion, 3 Hours	*Linseed Oil* Average Size of Oil Globules	*Cod Liver Oil* Appearance of Emulsion, 3 Hours	*Cod Liver Oil* Average Size of Oil Globules	*Castor Oil* Appearance of Emulsion, 3 Hours	*Castor Oil* Average Size of Oil Globules	*Mineral Oil* Appearance of Emulsion, 3 Hours	*Mineral Oil* Average Size of Oil Globules
4.0	Creaming	*A*	Stable	*A*	Stable	*B*	Stable	*B*
2.0	Creaming	*A*	Stable	*A*	Stable	*B*	Stable	*B*
1.0	Creaming	*A*	Stable	*A*	Creaming	*B*	Stable	*B*
0.6	Creaming	*A*	Stable	*A*	Creaming	*B*	.....	.....
0.4	Creaming	*A*	Creaming	*A*	Creaming	*B*	.....	.....
0.2	Creaming	*A*	Creaming	*A*	Oil sep.	*D*	Creaming	*B*
0.1	Creaming	*A*	Creaming	*A*	.....	.....	Creaming	*C*
0.05	Creaming	*A*	Creaming	*A*	Oil sep.	*D*	Creaming	*D*
0.025	Oil sep.	*A*	Oil sep.	*A*	.....	.....	Oil sep.	*D*
0.013	Oil sep.	*A*	Oil sep.	*A*	.....	.....	Oil sep.	*D*

[a] Number of parts used for 4 parts of oil and 2 parts of water.

for 4 parts of oil were allowed to stand for two weeks to observe their stability. There was creaming but no oil separation during two weeks of standing. Likewise, 4 ounces each of cod liver and linseed oil emulsions containing the same proportion of acacia were allowed to stand for two weeks, but during the 2-week period a teaspoonful of each emulsion, morning and night, was taken out after shaking. It was noticed that after 3 days of standing there was surface demulsification in both products, but the oil was readily emulsified on agitation. In the case of cod liver oil and linseed oil, the use of 0.05 part of acacia gave emulsions which would be acceptable for dispensing.

DISCUSSION OF RESULTS

Motor Stirrer.—The motor stirrer appeared to be of little value with cod liver oil, linseed oil and mineral oil. With respect to the average size of the oil globules, better emulsions were prepared by the mortar and pestle method. Only castor oil yielded a Grade *A* emulsion when using the motor stirrer.

Hand Egg Beater.—When using a hand egg beater to stir the primary emulsion, it was found that it produced just as good emulsions as triturating with a pestle with respect to stability of the preparation and the average size of the oil globules. It is more convenient to make emulsions with a mortar and pestle alone, since it takes less time to make these by avoiding washing of extra utensils.

Arnold Automatic Mixer.—When making emulsions in the Arnold automatic mixer using the Continental method, castor oil and mineral oil yielded Grade *A* products. No emulsions could be made with linseed oil and cod liver oil. Rees (3), likewise, could not make an emulsion of cod liver oil when using a malted-milk mixer even after 16 minutes of agitation. When using the English method, all the oils used yielded Grade *A* products. However, the linseed oil emulsion showed oil separation within a 3-hour period of standing; the cod liver, mineral and castor oil emulsions were stable over that period of time.

Fig. 1.—Mineral Oil Emulsions—Arnold Automatic Mixer (×430).

Fig. 2.—Castor Oil Emulsions—Arnold Automatic Mixer (×430).

Homogenizer.—Results on homogenization of the various oils showed that in the case of linseed oil and cod liver oil Grade *A* preparations were formed when using from 4 parts to 0.013 part of acacia for 4 parts of oil. The linseed oil emulsions showed creaming within a 3-hour period of standing. It was felt that 0.05 part of acacia in the case of these oils gave emulsions which would be acceptable for dispensing. Tice (4) showed that the hand homogenizer permitted cutting down the amount of acacia from 12.5% as used in a 50% oil-in-water emulsion prepared by the Continental method to 5 per cent. Rees (3) prepared cod liver oil emulsions by four different methods and found that the hand homogenizer produced the best emulsion.

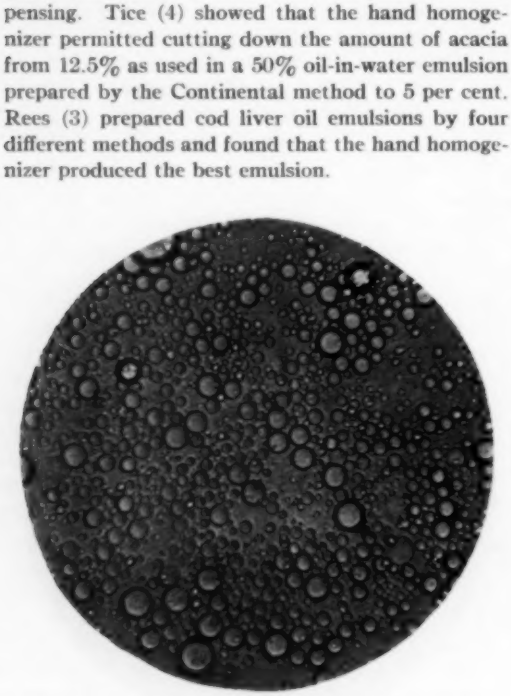

Fig. 3.—Castor Oil Emulsions—Homogenizer (×430).

Fig. 4.—Linseed Oil Emulsions—Homogenizer (×430).

Very little work has been done on homogenization of castor oil and mineral oil. Brown (5) studied the effect of homogenization on a mineral oil emulsion and an emulsion consisting of a mixture of magnesium hydroxide and liquid paraffin. The average diameter of the oil globules in unhomogenized samples was about 15 to 20 microns. Homogenization gave an average globule size from 2 to 5 microns. In the present investigation, homogenization of castor oil and mineral oil gave an average globule size of about 3.5 microns when larger proportions of acacia were used. However, for these oils the hand homogenizer did not seem to have much advantage over the mortar and pestle method of making emulsions. Although the homogenizer permitted emulsification with lower proportions of acacia, better emulsions, with respect to the average size of the oil globules, were produced with the mortar and pestle method when using one or more parts of acacia for 4 parts of oil. The fact that castor oil and mineral oil have a high viscosity may be one of the reasons why the homogenizer did not give as good emulsions in the case of these oils.

SUMMARY

A study was made of the efficiency of the Continental and English methods of emulsification as compared with the use of mechanical stirrers and a hand homogenizer for making emulsions.

The motor stirrer was inferior to the mortar and pestle method of making emulsions when using cod liver oil, linseed oil and mineral oil. Only castor oil yielded a Grade *A* product.

Stirring the primary emulsion with a hand egg beater produced just as good emulsions as the mortar and pestle method.

When making emulsions in the Arnold automatic mixer, using the Continental method, castor oil and mineral oil yielded Grade *A* products; no emulsions could be made with linseed oil and cod liver oil. When using the English method in the Arnold automatic mixer, all the oils studied yielded Grade *A* products; the linseed oil emulsion was the only one showing oil separation within a 3-hour period of standing.

Hand homogenization of cod liver oil and linseed oil emulsions produced Grade *A* products when using from 4 parts to 0.013 part of acacia for 4 parts of oil. The linseed oil emulsions showed creaming within a 3-hour period of standing. When using castor oil and mineral oil, the homogenizer permitted emulsification with lower proportions of acacia; however, better emulsions with respect to the average size of the oil

globules were produced by the mortar and pestle method when using one or more parts of acacia for 4 parts of these oils.

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(To be concluded.)

Hydrogenated Castor Oil in Ointments

VI. Sulfated Product in Official Ointments

*By George W. Fiero**

The first ointments were prepared from animal fats such as lard, horse fat, goose grease, etc. These fats were unsatisfactory from a pharmaceutical standpoint because they readily developed rancidity. Addition of preservatives such as benzoin retarded but did not prevent rancidity. The use of lard as an ointment base in the official ointments continued until the U. S. P. IX (1916) when petrolatum replaced it in most ointments.

The most widely employed base to-day is petrolatum, both for official ointments and individual prescriptions. This base is used largely because of the fact that it is stable and that it is compatible with most medicaments. Being a hydrocarbon, however, it definitely has no tendency to absorb water—not even as much as the natural fats. Because of this property, it is often used in conditions where it is contra-indicated. Certain types of dermatitis of the hands should not, as is often the case, be covered with a greasy ointment because this prevents evaporation of perspiration and may cause secondary infection.

Where there is perspiration or a serous discharge, it seems that they act as a barrier between the skin and the medicament in a petrolatum base. For such cases a hydrophilic ointment base is essential so that perspiration acts as a medium and not a barrier. Such a base should consist entirely, or in large part, of water-soluble material.

Mumford (1) states: "An ideal base would be one which acted with equal efficiency on dry and oily skins, which could be removed with water instead of olive oil or liquid paraffin, and which could suspend within itself water-soluble and fat-soluble chemicals and transfer them to the skin in a manner which vaseline cannot." He also pointed out that a base should be able to utilize perspiration and serous discharge instead of acting as a barrier to them as in the case of vaseline. Of course, there is doubt about the term "ideal ointment base" as in certain cases a non-hydrophilic occlusive base might be desired. Usually, however, a hydrophilic base is desirable.

There have been several suggestions made for hydrophilic ointment bases (2). The addition of cholesterin to petrolatum renders it capable of absorbing water. This type of base has been quite widely employed. Emulsions have likewise been employed. Many of these are satisfactory for certain medicaments but definitely unsatisfactory for substances such as salicylic acid, mercurials, etc., due to their alkalinity.

Unlike other vegetable oils, when castor oil is catalytically hydrogenated to an iodine number of less than 10, it is still capable of sulfation because of the presence of the hydroxyl radical. This product, sulfated (or sulfonated) hydrogenated castor oil (abbreviated "SHCO") is now being manufactured in commercial quantities.[1] It appears from clinical data to meet Mumford's specifications for an ideal ointment base. It has the consistency of an ointment, unlike other sulfated oils which are liquid. Unlike petrolatum, it is soluble in water and has a body and color similar to that of wool fat. The consistency varies, of course, with the extent of sulfation; the material used in these experiments possessed the following characteristics:

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[1] Manufactured by National Oil Products Co., Harrison, N. J.

Melting point	41.5° C.
Softening point	30.0° C.
SO_3 content	10%
p_H (5% solution)	6.0–6.3

The fact that it has a p_H of 6, very slightly on the acid side, is valuable because this is approximately the p_H of the skin (3). Also, it makes an ideal vehicle for substances such as salicylic acid which are not readily compatible with bases of an alkaline nature.

Its solubility in water is a distinct advantage. Perspiration does not interfere with the ointment as, for example, it would in the case of official Whitfield's Ointment. It may be readily incorporated with many substances which are not soluble or readily suspended in other ointment bases. Also, it incorporates readily with aqueous, alcoholic, glycerin, glycol, liquid petrolatum, etc., solutions without precipitation, as well as other bases such as petrolatum, fats, spermaceti, wax, etc. Of minor dispensing importance is the fact that apparatus used to prepare ointments may be readily cleansed with water. Likewise any excess ointment can be removed from the skin with water.

Because it is made from completely hydrogenated castor oil, free from unsaturated fatty acids, it is not subject to rancidity. Clinical Patch tests in two clinics indicate that it is non-irritating, thus well suited for an ointment base. Like other sulfated oils it possesses wetting properties. This should make it more readily absorbed by the skin. Likewise it possesses definite detergent properties, either alone or with added petrolatum to give it an oily consistency.

EXPERIMENTAL

Official Ointments.—SHCO can be used as an ointment base without addition of other substances if an adhesive ointment is desired. The material possesses a peculiar stickiness which is very advantageous when it is desired to produce an ointment which will adhere to the skin. This ointment is often applied after the skin has been moistened with water or a small amount of water may be rubbed into the ointment after it has been applied to the skin.

Preliminary tests indicated that medicaments could be readily incorporated with SHCO using manipulation with a spatula and pill tile, trituration in a mortar and trituration with previously melted SHCO. All three methods were satisfactory. Trituration with fused SHCO was the simplest method and therefore used in all cases unless otherwise specified; for dispensing, however, it might be less trouble to use the SHCO cold. When incorporating with medicaments, it was sometimes not necessary to use the solvent employed by the official formula. In all cases a small amount of the base or the diluent was incorporated with the medicament and then the balance of the base added. Rapid trituration or use of a mechanical mixer produced a lighter colored ointment due to incorporation of air. Since SHCO in most cases needed no additional solidifiers, such as wax, in large scale manufacture, the ointments could be poured while hot and allowed to cool in ointment jars without danger of separation of solidifier or the medicament which in most cases was well suspended or dissolved in the base.

For many ointments, however, a smooth, less adhesive ointment is desired. The stickiness can be removed by the addition of many substances, thus any desired ointment base can be obtained. Among such substances are petrolatum, liquid petrolatum, fats and fixed oils, glycerin, glycols or water. If the resultant ointment is too soft, it may be made stiffer by addition of solidifiers such as wax, spermaceti, hydrogenated castor oil, hydroxystearic acid, stearic acid, etc.

In most cases the medicament readily incorporates with the SHCO-petrolatum mixture. Often, however, slightly better dispersion is obtained if the material is triturated with the SHCO and the petrolatum added. The amount of petrolatum may vary with the individual ointment. Twenty-five per cent of petrolatum makes a smooth ointment; even though as little as twenty-five per cent of SHCO is employed, the ointment is still hydrophilic and may be readily removed with water.

For many purposes an emulsified ointment base is indicated. SHCO is a good emulsifying base and numerous types of emulsified creams can be prepared. The simplest type may be made by melting 28.5 parts each of SHCO and petrolatum and adding 43 parts of water, heated to the same temperature. Agitation results in a very good emulsion which is compatible with most medicaments. Other creams may be prepared using substances such as diethylene glycol monostearate, glyceryl monostearate, triethanolamine and its soaps, etc.

If making ointments with this emulsified cream, in many cases the emulsified ointment base will readily incorporate the medicament. In other cases, the medicament may be dissolved in the water or, in the case of substances such as coal tar, incorporated first with the SHCO.

Formulas are given for the three types of ointments, using the official formula modified only in that the SHCO bases replace the official base. In the following list of formulas, the one marked "1" is an adhesive base; "2" is a smooth base; and "3" is an emulsified base. In many cases the preparation can be prepared by merely incorporating the medicament with the appropriate simple ointment

and different formulas are not necessary. For large-scale manufacturing, however, a slightly better ointment often results if the material (unless soluble in the amount of water in the cream base) is first incorporated with the SHCO and then the petrolatum and, if a cream base, the water incorporated. The SHCO tends to suspend insoluble substances better such as zinc oxide, mercurial salts, etc.

OFFICIAL OINTMENTS (U. S. P.)

Simple Ointment: 1 Sulfated hydrogenated castor oil.

2 SHCO 75 Gm., white petrolatum 25 Gm. Triturate the bases, with or without previously melting them.

3 SHCO 28.5 Gm., white petrolatum 28.5 Gm., distilled water 45 Gm. Melt the SHCO and petrolatum, heat the water to the same temperature and added to the molten bases with agitation.

Boric Acid Ointment: Boric acid 10 Gm., simple ointment 90 Gm. Triturate the acid with the simple ointment, with or without fusion.

Tannic Acid Ointment: Tannic acid 20 Gm., Glycerin 20 Gm., simple ointment 60 Gm. Triturate the acid with the glycerin, incorporate the molten simple ointment. (This ointment was not satisfactory when made with the emulsified base.)

Belladonna Ointment: 1. Pilular extract of belladonna 10 Gm., SHCO 90 Gm. Triturate the extract with a small amount of the molten SHCO, gradually incorporating the balance.

2. Pilular extract of belladonna 10 Gm., SHCO 67.5 Gm., petrolatum 22.5 Gm. Triturate the extract with a small amount of the molten SHCO, gradually incorporating the balance and the molten petrolatum.

3. Pilular extract of belladonna 10 Gm., SHCO 25.5 Gm., petrolatum 25.5 Gm., distilled water 39 cc. Triturate the belladonna with a small amount of the molten SHCO, following with the balance and the molten petrolatum. Heat the water to approximately the same temperature and add it to the mixture with trituration.

Chrysarobin Ointment: 1. Chrysarobin 6 Gm., chloroform 4 Gm., liquid petrolatum 6 Gm., SHCO 84 Gm. Triturate the chrysarobin with the liquid petrolatum and the chloroform, add the molten SHCO and triturate.

2. Chrysarobin 6 Gm., chloroform 4 Gm., petrolatum 22.5 Gm., SHCO 67.5 Gm. Triturate the chrysarobin with the molten petrolatum and chloroform, add the molten SHCO and triturate.

3. Chrysarobin 6 Gm., simple ointment 94 Gm. Triturate.

Nutgall Ointment: Nutgall 20 Gm., glycerin 20 Gm., simple ointment 60 Gm. Triturate the nutgall with the glycerin, incorporate the molten simple ointment. (This ointment was not satisfactory when made with the emulsified base.)

Ammoniated Mercury Ointment: Ammoniated mercury 10 Gm., simple ointment 90 Gm. Triturate.

Strong Mercurial Ointment: Mercury 50 Gm., oleate of mercury 2 Gm., simple ointment 48 Gm. Triturate the mercury with the oleate until dispersed, incorporate the simple ointment.

Mild Mercurial Ointment: Strong mercurial ointment 60 Gm., simple ointment 40 Gm. Triturate.

Yellow Mercuric Oxide Ointment: Yellow mercuric oxide 1 Gm., liquid petrolatum 1 Gm., simple ointment 98 Gm. Triturate the oxide with the liquid petrolatum until smooth, incorporate with the simple ointment.

Iodine Ointment: 1. Iodine 4 Gm., potassium iodide 4 Gm., glycerin 12 Gm., SHCO 80 Gm. Dissolve the potassium iodide in the glycerin, triturate with the iodine until dissolved, and incorporate with the SHCO. A stiffer ointment may be prepared by dissolving the potassium iodide in 92 Gm. molten SHCO, followed by the iodine, with no glycerin.

2. Iodine 4 Gm., potassium iodide 4 Gm., glycerin 12 Gm., SHCO 60 Gm., petrolatum 20 Gm. Prepare as above; a stiffer ointment can also be prepared as above; the petrolatum should be incorporated last.

3. Iodine 4 Gm., potassium iodide 4 Gm., distilled water 40 cc., SHCO 26 Gm., petrolatum 26 Gm. Dissolve the potassium iodide in the water; dissolve the iodine in this solution. Melt the SHCO and petrolatum and incorporate the aqueous solution.

Phenol Ointment: Phenol 2 Gm., simple ointment 98 Gm. Incorporate.

Pine Tar Ointment: 1–2. Pine tar 50 Gm., yellow wax 20 Gm., simple ointment 30 Gm. Melt the wax and add to the previously warmed simple ointment. Incorporate the pine tar, previously warmed.

3. Pine tar 50 Gm., yellow wax 20 Gm., SHCO 8.5 Gm., petrolatum 8.5 Gm., water 13 cc. Melt the wax and petrolatum. Mix the molten SHCO with warm pine tar. Mix them and incorporate the water.

Sulfur Ointment: Sulfur 15 Gm., simple ointment 85 Gm. Triturate with or without melting the simple ointment.

Zinc Oxide Ointment: 1. Zinc oxide 20 Gm., SHCO 55 Gm., water 25 cc. Triturate the zinc oxide with the molten SHCO, incorporate the water.

2. Zinc oxide 20 Gm., SHCO 41 Gm., petrolatum 14 Gm., water 25 cc. Triturate the zinc oxide with the molten SHCO, incorporate the molten petrolatum and finally the water.

3. Zinc oxide 20 Gm., simple ointment 80 Gm. Triturate.

OFFICIAL OINTMENTS (N. F.)

Compound Ointment of Benzoic Acid: Benzoic acid 12 Gm., salicylic acid 6 Gm., simple ointment 82 Gm. Triturate the acids with the molten base. (This ointment was not satisfactory when prepared with the emulsified base.)

Calamine Ointment: 1. Prepared calamine 15 Gm., SHCO 65 Gm., water 25 cc. Triturate the calamine with the molten SHCO, incorporate the water.

2. Prepared calamine 15 Gm., SHCO 64 Gm., petrolatum 21 Gm. Triturate the calamine with the molten SHCO and incorporate the molten petrolatum.

Modification (similar to N. F. VII): Prepared calamine 15, SHCO 45, petrolatum 15, compound spirit of rose geranium 1 cc., distilled water 25 cc. Triturate the ingredients in the order named, melting the bases.

3. Prepared calamine 15, simple ointment 85. Triturate.

Camphor Ointment: Camphor 22 Gm., alcohol *q. s.*, simple ointment 78 Gm. Powder the camphor with the alcohol, allow the latter to evaporate and incorporate with the base. (In the case of "2" and "3," the camphor may be dissolved without alcohol treatment, in the warm, molten petrolatum.)

Capsicum Ointment: Oleoresin of capsicum 5 Gm., simple ointment 95 Gm. Incorporate.

Mild Mercurous Chloride Ointment: Mild mercurous chloride 30 Gm., simple ointment 70 Gm. Triturate.

Colloidal Mercurous Chloride Ointment: Magma of colloidal mercurous chloride 30 Gm.,[2] simple ointment 70 Gm. Incorporate.

Mercuric Nitrate Ointment, Half-Strength: Mercuric nitrate ointment 50 Gm., simple ointment 50 Gm. Incorporate. (This ointment is commonly employed by the dermatologist in half strength; dilution with SHCO makes a hydrophilic ointment.)

Red Mercuric Oxide Ointment: Red mercuric oxide 10 Gm., simple ointment 90 Gm. Triturate.

Ichthammol Ointment: Ichthammol 10 Gm., simple ointment 90 Gm. Incorporate.

Stainless Iodized Ointment: Iodine 5 Gm., oleic acid 20 Gm., simple ointment 75 Gm. Warm the iodine with the oleic acid until the red color disappears, incorporate with the simple ointment.

Compound Menthol Ointment: Menthol 10 Gm., methyl salicylate 10 Gm., white wax 10 Gm., simple ointment 70 Gm. Melt the wax, incorporate it with the warmed simple ointment. Dissolve the menthol in the methyl salicylate and incorporate with the base.

Coal Tar Ointment: 1. Coal tar 5 Gm., SHCO 95 Gm. Incorporate with the molten SHCO.

2. Coal tar 5 Gm., SHCO 71 Gm., petrolatum 24 Gm. Incorporate the coal tar with the molten SHCO; incorporate the petrolatum.

3. Coal tar 5 Gm., SHCO 27 Gm., petrolatum 27 Gm., distilled water 41 cc. Triturate the coal tar with the molten SHCO, add the molten petrolatum, mix and triturate with the water, previously warmed.

Compound Tar Ointment: 1–2. Rectified oil of tar 4 Gm., tincture of benzoin 2 Gm., zinc oxide 3 Gm., simple ointment 91 Gm. Triturate the zinc oxide with the molten base, incorporate the oil and the tincture.

[2] Courtesy of Research Dept., The Upjohn Co., Kalamazoo, Michigan.

3. Rectified oil of tar 4 Gm., tincture of benzoin 2 Gm., oxide of zinc 3 Gm., SHCO 26 Gm., petrolatum 26 Gm., water 39 cc. Triturate the zinc oxide with molten SHCO, incorporate the tincture, oil and molten petrolatum, finally the water, previously warmed.

Ointment of Potassium Iodide: Potassium iodide 10 Gm., sodium thiosulfate 1 Gm., distilled water 9 Gm., simple ointment 80 Gm. Dissolve the salts in water; incorporate with the simple ointment. (A stiffer ointment may be prepared by triturating the salts with SHCO, using no water, and incorporating the petrolatum in the case of "2." This ointment was not satisfactory when prepared with the emulsified base.

Compound Resorcinol Ointment: Resorcinol, zinc oxide, bismuth subnitrate, rectified oil of birch tar, of each 6 Gm., wax 6 Gm., simple ointment 70 Gm. Triturate the solids with warm simple ointment; incorporate the oil and the melted wax.

Scarlet Red Ointment: Scarlet red 5 Gm., simple ointment 95 Gm. Triturate.

Mustard Ointment: Volatile oil of mustard 2 Gm., simple ointment 98 Gm. Incorporate.

Stramonium Ointment: 1. Pilular extract of stramonium 10 Gm., SHCO 90 Gm. Triturate.

2. Pilular extract of stramonium 10 Gm., SHCO 74 Gm., petrolatum 21 Gm. Triturate the extract with the SHCO, incorporate the petrolatum.

3. Pilular extract of stramonium 10 Gm., SHCO 25.5 Gm., petrolatum 25.5 Gm., distilled water 39 cc. Triturate the extract with molten SHCO, add the molten petrolatum and incorporate the water, previously warmed.

Alkaline Sulfur Ointment: This ointment was not satisfactory when prepared with the emulsified base.

Compound Sulfur Ointment: Precipitated calcium carbonate 10 Gm., sublimed sulfur 15 Gm., juniper tar 15 Gm., simple ointment 60 Gm. Triturate.

Zinc Stearate Ointment: Zinc stearate 35 Gm., liquid petrolatum 10 Gm., simple ointment 55 Gm. Mix the liquid petrolatum with the warm simple ointment, and incorporate the zinc stearate by trituration. If a stiffer ointment is desired, the liquid petrolatum may be replaced by simple ointment.

DISCUSSION

The above formulas merely serve to indicate the compatibility of SHCO as an ointment base. In some cases the ointment might not be stiff enough for warm climates; this can be remedied by addition of a solidifier such as wax.

Ointments prepared with SHCO are usually much easier to prepare than the official ointment. In most cases the medicaments may be incorporated with the SHCO

base without regard to proper pharmaceutical technique.

SHCO can be used to overcome incompatibilities; coal tar or balsam of peru, for instance, previously triturated with SHCO may readily be incorporated with petrolatum, lard, lanolin, etc.

The emulsified base is an oil-in-water emulsion. This is a distinct advantage as such an emulsion would absorb perspiration or serous fluid better than a water-in-oil emulsion. A less greasy base (semi-vanishing) may be obtained by substituting diethylene glycol monostearate up to about 50% of the SHCO.

Ointments prepared with SHCO are recommended particularly in cases where there is serous discharge or perspiration, or in cases where a washable ointment is indicated. An example of the latter is scalp ointments; SHCO ointments have proved very satisfactory for this purpose since they are readily removed by simple washing with water.

SUMMARY

Sulfated hydrogenated castor oil is recommended as an ointment base. It is water-soluble, semi-solid, compatible with medicaments used in ointments and produces, when used in quantities of twenty-five per cent or more, hydrophilic ointments. An emulsified base comprised of sulfated hydrogenated castor oil, petrolatum and water is described. Formulas are given for the official ointments prepared with adhesive base, smooth base and emulsified base.

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"When the archer misses the center of the target, he turns around and seeks for the cause of his failure within himself."—Kong Fu Tsze.

Book Reviews

A New Dictionary of Chemistry, edited by STEPHEN MIALL. 544 pages. Longmanns, Green & Co. Price, $15.00.

This dictionary is intended for both chemist and layman and it provides a reference source of chemical terms and facts relating to chemicals and drugs for use in special fields. It contains a vast number of entries which include the latest advances in chemistry, inorganic, organic and physical. Many of the entries include references to books and papers in which further information can be found. Trade names are included in many cases. There are many short biographical sketches of eminent chemists in which their outstanding achievements are given. The volume also contains a classified reading list of 85 volumes and a table of physical constants of organic compounds.—A. G. D.

Handbook for Chemical Patents, by EDWARD THOMAS. 270 pages, 5½ x 8¼. 1940. New York: Chemical Publishing Company. Price, $4.00.

The author of this book is a former employee of the U. S. Patent Office and is, therefore, well qualified to explain the essential details of patent procedures, which he has done. Included in the explanations are suggestions for writing patent specifications, anticipation of a patent based on previous facts, types of infringement, process of taking out a patent from the patent office, assignments, licenses, etc. Explanatory references to cases are numerous. The book should prove to be an invaluable aid to those seeking to obtain a patent on a chemical process or composition of matter.—A. G. D.

The Essentials of Physiology and Pharmacodynamics, by GEORGE BACHMANN and A. RICHARD BLISS, JR. 3rd Edition. xiv + 508 pages, 6½ x 10. 1940. Philadelphia: The Blakiston Co. Price, $4.50.

This, the third edition of this well-known textbook on physiology and pharmacodynamics, follows along the lines of preceding editions. The anatomic viewpoint is maintained and the pharmacologic activity of drugs is explained at the appropriate point. This edition includes the newer drugs, such as ergonovine, sulfapyridine, etc.—A. G. D.

Mathematics in Bacteriology, by OTTO RAHN. ii + 63 pages, 8¼ x 10¾. 1939. Minneapolis: Burgess Publ. Co. Price, $1.75.

This book gives the application of mathematics to the interpretation of such subjects as cell division and growth, unrestricted and restricted multiplication and fermentation, and the death rate in disinfection. The probable error computed on a statistical basis and the use of graphs are discussed. It contains a sufficient amount of elementary calculus and information on the use of graphs to enable

the student to make these applications. The book should serve to point out the possibilities of the mathematical treatment of certain biological processes.—A. G. D.

Synopsis of Materia Medica, Toxicology and Pharmacology, by F. R. DAVISON. 633 pages, 4¾ x 7⅝. 1940. St. Louis: C. V. Mosby Co. Price, $5.00.

This book is designed for students and practitioners of medicine. The first portion treats of the principles of drug action, methods of administration of drugs, modification of their action, sources, types, standards, classification of drugs, etc. There is also a chapter on prescription writing and one on toxicology. Part II deals with the drugs used by the physician. These are classified according to their action on the body. In addition to the action, use and dose of the various drugs, there is frequently given one or more prescriptions indicating the practical application of the drug. This enables the physician to make immediate use of the material presented and also makes the volume one which may be included to advantage in a pharmaceutical library.—A. G. D.

Forensic Chemistry, by HENRY T. F. RHODES. 214 pages. Chemical Publishing Co., Inc., 148 Lafayette St., New York, N. Y., 1940. Price, $5.00.

The author stated that the purpose of this book is to collect in one volume information on forensic chemistry which has appeared in criminological journals and to provide an outline for the operating of a forensic chemical laboratory. The book is divided into two parts. Part I deals with the application of chemical methods to the identification of persons. The identification of persons by indirect means is discussed, *e. g.*, by means of dust particles, starch, shellac and other materials which may be found on a person and from which a clue as to their occupation or the habits of a person may be obtained. Part II is devoted to a discussion of the chemical methods for the proof of "*corpus delicti*." The examination of stains, weapons, documents, poisons, etc., is also discussed. There is a chapter devoted to questioned documents, others on firearms, explosives, counterfeit money and the examination of toxic materials. At the end of the book there is a bibliography of several pages. The book contains considerable information from the personal experience of the author and should prove a valuable addition to the limited number of books now available on this subject.—A. G. D.

What Are the Vitamins? by WALTER H. EDDY. 247 pages. Reinhold Publishing Corp., 330 West 42nd St., New York, N. Y., 1941. Price, $2.50.

This book contains pertinent and reliable information based on original investigation and a review of the literature. It answers such questions as: What are the vitamins? What do they do? Which one do I need? How much of each do I need? Where and how can I get them? In the two opening chapters supplemented by tables of potency, unit equivalents and the chemical nature of vitamins and vitamin values of foods, the vitamins are defined as organic chemical compounds and the function of these substances as prosthetic groups in enzyme system controlling respiration and intracellular metabolism is explained. The remaining eleven chapters are devoted to the functions of each vitamin. The treatment is mainly pathological and is concerned chiefly with the diagnosis, clinical manifestations and treatment. There is a bibliography at the end of each chapter. The book is believed to be of particular value to the physician and pathologist, also the worker in the field of nutrition. —A. G. D.

The Chinese Way in Medicine, by EDWARD H HUME. 189 pages. 5½ x 7¾. The Johns Hopkins Press, Baltimore, Md., 1940. Price $2.25.

In this book the author has succeeded in bringing out the important philosophies of Chinese medicine and in presenting an interesting commentary upon the leading Chinese physicians of ancient times and on the drugs employed by them. Among the physicians mentioned are Fu Hsi, a contemporary of the great Imhotep of Egypt, Shên Nung, the father of Chinese medicine and the compiler of Pên Ts ào, the original Chinese pharmacopœia, and Huang Ti, who introduced methods of diagnosis and physical therapy. Attention is also called to the fact that many of our present-day drugs are mentioned in the Pên Ts áo, the best known of which is probably ephedra from which ephedrine is obtained. It is also noted that such important drugs as kaolin, chaulmoogra oil, stramonium, etc., are listed in the Pên Ts ào Kang Mu, a catalogue of native herbs compiled by Li Shih-Chên during the Ming dynasty. The book contains much valuable information on the history of Chinese medicine and is worthy of a place in all medical and pharmaceutical libraries.—A. G. D.

NOTICE

It will be appreciated if any one, who has a copy of the January 1940 issue of the Scientific Edition that he does not need, will mail it to the AMERICAN PHARMACEUTICAL ASSOCIATION, 2215 Constitution Ave., Washington D. C., as our supply of this number has been exhausted.